

Filed 31-December-2001

*In the United States Patent and Trademark Office***PATENT APPLICATION****TITLE:****METHOD FOR TREATING FIBROTIC
DISEASES OR OTHER INDICATIONS ID****INVENTOR(s):**

John Egan
Dilip Wagle
Sara Vasan
Martin Gall
Stanley Bell
Edmond J. LaVoie

401 PCT/US2003/007004

**METHOD FOR TREATING FIBROTIC DISEASES OR OTHER INDICATIONS
ID**

5 This application claims the priority of Serial No. 60/296,435, filed 6-Jun-2001, Serial No. 60/259,242, filed 2-Jan-2001, and Serial No. 60/259,431, filed 29-Dec-2000, and is a continuation of Serial No. 09/905,188, filed 12-Jul-2001.

10 The present invention relates to methods for treating certain fibrotic diseases or other indications, and to compounds and compositions for use in such treating.

15 Glucose and other sugars react with proteins by a non-enzymatic, post-translational modification process called non-enzymatic glycosylation. At least a portion of the resulting sugar-derived adducts, called advanced glycosylation end products (AGEs), mature to a molecular species that is very reactive, and can readily bind to amino groups on adjacent proteins, resulting in the formation of AGE cross-links between proteins. Recently a number of classes of compounds have been identified whose members inhibit the formation of the cross-links, or in some cases break the cross-links. These compounds include, for example, the thiazolium compounds described in US Patent No. 5,853,703. As AGEs, and particularly the resulting cross-links, are linked to several degradations in body function linked with diabetes or age, these compounds 20 have been used, with success, in animal models for such indications. These indications include loss of elasticity in blood vasculature, loss of kidney function and retinopathy.

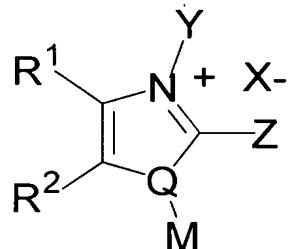
25 Now, as part of studies on these compounds, it has been identified that these compounds inhibit the formation of bioactive agents, such as growth factors and inflammatory mediators, that are associated with a number of indications. These agents include vascular endothelial growth factor (VEGF) and TGF[beta]. As a result, a number of new indications have been identified for treatment with agents that inhibit the formation of, or more preferably break, AGE-mediated cross-links. It is not unreasonable to infer that the effects seen are due to the removal of AGE-related molecules that provide a stimulus for the production or release of these growth factors. 30 Removal of such molecules is believed to proceed in part due to the elimination of AGE-related cross-links that lock the AGE-modified proteins in place. Moreover, such compounds also reduce the expression of collagen in conditions associated with excess collagen production. Regardless of the mechanism, now provided are new methods of treating a number of indications.

100-1331-510A

Summary of the Invention

In one embodiment, the invention relates to a method of treating or ameliorating or preventing an indication of the invention in an animal, including a human comprising

5 administering an effective amount of a compound of the formula I:

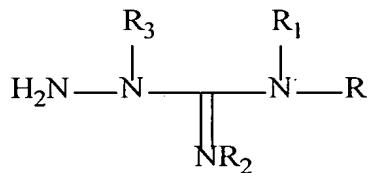


(I)

wherein the substituent groups are defined below. The invention also relates to compounds of formula I.

10 The compounds used in the methods described here are first agents, which are those described with reference to formula I, or second agents, which are aminoguanidine or those compounds described with reference to formula I. The second agents can be used as an adjunct to treatment with a first agent, or as the primary effective agent where noted.

15 Second agents are aminoguanidine or a compound of the aminoguanidine class of formula A



(A)

wherein R is an alkyl group, or a group of the formula $-N(R^4)(R^5)$ wherein R^4 is hydrogen, and R^5 is an alkyl group or a hydroxyalkyl group; or R^4 and R^5 together with

20 the nitrogen atom are a heterocyclic group containing 4-6 carbon atoms and, in addition to the nitrogen atom, 0-1 oxygen, nitrogen or sulfur atoms; R^1 is hydrogen or an amino group; R^2 is hydrogen or an amino group; R^3 is hydrogen or an alkyl group, wherein R and R^1 cannot both be amino groups. Preferably at least one of R^1 , R^2 , and R^3 is other than hydrogen. The compounds can be used as their pharmaceutically acceptable acid

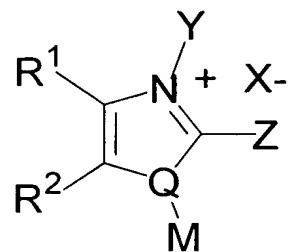
addition salts, and mixtures of such compounds. When aminoguanidine compounds are administered, they can be administered by any route of pharmaceutical administration including those discussed below for other first agents.

5

Detailed Description of the Invention

Provided is a method of treating or ameliorating an indication of the invention in an animal, including a human, comprising administering an effective amount of (A) a compound of the formula I:

10



(I)

wherein

a. R¹ and R² are

1. independently selected from hydrogen, acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C₁-C₃)alkylenedioxy, allyl, amino, ω -alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, hydroxy, (C₂-C₆)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylsulfonyl, alkylsulfinyl, alkylthio, trifluoromethyl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, 4-[C₆ or C₁₀]arylpiperidin-1-yl, 4-[C₆ or C₁₀]arylpiperazin-1-yl, Ar {wherein, consistent with the rules of aromaticity, Ar is C₆ or C₁₀ aryl or a 5- or 6-membered heteroaryl ring, wherein 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring can be fused to a benzene, pyridine, pyrimidine, pyridazine, pyrazine, or (1,2,3)triazine (wherein the ring fusion is at a carbon-carbon double bond of Ar)(or wherein Ar is as above but not heteroaryl fused to pyridine)(in one embodiment, Ar is C₆ or C₁₀ aryl)}, Ar-alkyl, Ar-O, ArSO₂-,

ArSO-, ArS-, ArSO₂NH-, ArNH, (N-Ar)(N-alkyl)N-, ArC(O)-, ArC(O)NH-, ArNH-C(O)-, and (N-Ar)(N-alkyl)N-C(O)-, or together R₁ and R₂ comprise methylenedioxy (in one embodiment, independently selected from hydrogen, acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, 5 alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, (C₁-C₃)alkylenedioxy, allyl, ω -alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl, cycloalkyl, halo, hydroxy, (C₂-C₆)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylsulfonyl, alkylsulfinyl, alkylthio, trifluoromethyl, Ar, Ar-alkyl, Ar-O, ArSO₂-, ArSO-, ArS-, ArSO₂NH-, ArNH, (N-Ar)(N-alkyl)N-, ArC(O)-, 10 ArC(O)NH-, ArNH-C(O)-, and (N-Ar)(N-alkyl)N-C(O)-); or

2. together with their ring carbons form a C₆- or C₁₀- aromatic fused ring system; or

3. together with their ring carbons form a C₅-C₇ fused cycloalkyl ring having up to 15 two double bonds including any fused double bond of the -olium or -onium containing ring, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxycarbonyl, amino, aminocarbonyl, carboxy, fluoro, or oxo substituents (in one embodiment, the substitutions do not include amino); or

4. together with their ring carbons form a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring may be optionally substituted with one or more 1-pyrrolidinyl-, 4-[C₆ or C₁₀]arylpirperazin-1-yl, 4-[C₆ or C₁₀]arylpirperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C₁-C₃)alkylenedioxy groups (in one embodiment, the optional substitutions, which are in addition to the general substitutions recited 20 below, are one or more halo or (C₁-C₃)alkylenedioxy groups); or

25 5. together with their ring carbons form a five to eight membered heterocycle, wherein the heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, and S(O)_n, where n=0,1, or 2;

30 b. Z is

1. hydrogen, alkyl, Ar—CH₂;

RECEIVED JULY 23 2000

2. a group of the formula $-NR^3R^4$, wherein R^3 and R^4 may be independently hydrogen, alkyl, Ar, or Ar—alkyl-;

3. a group of the formula $-CH(OR^{11})R^{12}$, wherein R^{11} is hydrogen, methyl, ethyl or $CH_3C(O)-$; and R^{12} is $[C_1$ to $C_6]$ alkyl, Ar, or CO_2R^{13} wherein R^{13} is hydrogen methyl or ethyl;

5 4. a group of the formula $-C(CO_2R^{13})(OR^{11})R^{12}$

5 5. a group of the formula $-CH_2WAR$, wherein W is $-(C=O)-$ or $-S(O)_n-$ where $n=1$ or 2; or

5 6. a group of the formula $-CH_2C\equiv CR^{14}$, wherein R^{14} is $(C_1$ - $C_6)$ alkyl;

10 c. Y is

1. amino, or

2. a group of the formula $-CH(R^5)-R^6$ wherein

15 (a) R^5 is hydrogen, alkyl-, cycloalkyl-, alkenyl-, alkynyl-, aminoalkyl-, dialkylaminoalkyl-, $(N-[C_6$ or $C_{10}])aryl(N-alkyl)aminoalkyl-$, piperidin-1-ylalkyl-, pyrrolidin-1-ylalkyl, azetidinylalkyl, 4-alkylpiperazin-1-ylalkyl, 4-alkylpiperidin-1-ylalkyl, 4-[C_6 or $C_{10}])aryl$ piperazin-1-ylalkyl, 4-[C_6 or $C_{10}])aryl$ piperidin-1-ylalkyl, azetidin-1-ylalkyl, morpholin-4-ylalkyl, thiomorpholin-4-ylalkyl, piperidin-1-ylalkyl, $[C_6$ or $C_{10}])aryl$, or independently the same as R^6 (in one embodiment, hydrogen or alkyl);

20 (b) R^6 is

(1) hydrogen, alkyl (which can be substituted by alkoxy carbonyl), alkenyl, alkynyl, cyano- or Rs , wherein Rs is a C_6 or C_{10} aryl or a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or

25 (2) a group of the formula $-W-R^7$, wherein R^7 is alkyl, alkoxy, hydroxy or Rs , wherein W is $-C(=O)-$ or $-S(O)_n-$ where $n=1$ or 2;

(3) a group of the formula $-W-OR^8$ wherein R^8 is hydrogen or alkyl,

(4) a group of the formula $-CH(OH)Rs$; or

(5) a group of the formula $-W-N(R^9)R^{10}$, wherein

30 [a] R^9 is hydrogen and R^{10} is an alkyl or cycloalkyl, optionally substituted by

(i) $[C_6$ or $C_{10}])aryl$, or

5

10

15

20

25

30

(ii) a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, said heteroaryl ring can be optionally substituted with one or more 1-pyrrolidinyl, 4-[C₆ or C₁₀]arylpiperazin-1-yl, 4-[C₆ or C₁₀]arylpiperidin-1-yl, azetidin-1-yl, and morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C₁-C₃)alkylenedioxy groups, or fused to a phenyl or pyridine ring, wherein the ring fusion is at a carbon-carbon double bond of the heteroaryl ring (in one embodiment, the optional substitutions are one or more halo or (C₁-C₃)alkylenedioxy groups, or fused to a substituted phenyl), or

(iii) a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or

[b] R⁹ is hydrogen or lower alkyl and R¹⁰ is Ar; or

[c] R⁹ is hydrogen or lower alkyl, and R¹⁰ is a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms are selected from the group consisting of oxygen, nitrogen and sulfur, said heterocycle; or

[d] R⁹ and R¹⁰ are both alkyl groups; or

[e] R⁹ and R¹⁰ together with N form a heterocycle containing 4-10 ring atoms which can incorporate up to one additional heteroatom selected from the group of N, O or S in the ring, wherein the heterocycle is optionally substituted with (C₆-or C₁₀)aryl, (C₆-or C₁₀)arylalkyl, or a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each such heteroaryl can be optionally substituted with one or more 1-pyrrolidinyl, 4-[C₆ or C₁₀]arylpiperazin-1-yl, 4-[C₆ or C₁₀]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C₁-

C_3 alkylenedioxy (in one embodiment, the optional substituents to the heteroaryl are one or more halo or (C_1-C_3) alkylenedioxy); or

[f] R^9 and R^{10} are both hydrogen;

d. Q is N, O or S;

5 e. M is absent when Q is O or S;

f. M is alkyl, vinyl or allyl, or independently the same as Y; and

g. X is a pharmaceutically acceptable anion, or

(B) a pharmaceutically acceptable salt of the compound,

wherein aryl or Ar can be substituted with, in addition to any substitutions specifically

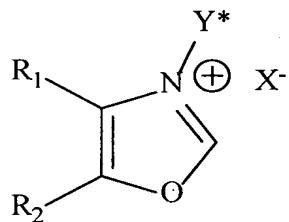
10 noted, one or more general substituents selected from the group consisting of acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C_1-C_3) alkylenedioxy, alkylsulfonyl, alkylsulfinyl, ω -alkylenesulfonic acid, alkylthio, allyl, amino, $ArC(O)$ -, $ArC(O)NH$ -, ArO -, Ar-, Ar-alkyl-, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, trifluoromethyl, hydroxy, (C_2-C_6) hydroxyalkyl, mercapto, 15 nitro, sulfamoyl, sulfonic acid, 1-pyrrolidinyl, 4-[C_6 or C_{10}]arylpiperazin-1-yl-, 4-[C_6 or C_{10}]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl (the "Aryl General Substituents") (in one embodiment, aryl or Ar can be substituted with, in addition to any substitutions specifically noted, one or 20 more general substituents selected from the group consisting of acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, (C_1-C_3) alkylenedioxy, alkylsulfonyl, alkylsulfinyl, ω -alkylenesulfonic acid, alkylthio, allyl, $ArC(O)$ -, $ArC(O)NH$ -, ArO -, Ar-, Ar-alkyl-, carboxy, carboxyalkyl, cycloalkyl, halo, trifluoromethyl, hydroxy, (C_2-C_6) hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid (the "Aryl Preferred 25 General Substitutions")); and

wherein heterocycles, except those of Ar, can be substituted with, in addition to any substitutions specifically noted, the following general substitutions: acylamino, alkanoyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, alkylsulfonyl, alkylsulfinyl, alkylthio, amino, $ArC(O)$ -, ArO -, Ar-, carboxy, dialkylamino, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, sulfamoyl, or trifluoromethyl (the "Heterocycle General Substituents") (in one embodiment,

heterocycles, except those of Ar, can be substituted with, in addition to any substitutions specifically noted, the following general substitutions: acylamino, alkanoyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylsulfonyl, alkylsulfinyl, alkylthio, ArC(O)-, ArO-, Ar-, carboxy, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, sulfamoyl, or trifluoromethyl (the "Heterocycle Preferred General Substituents").

In one embodiment, the compound of formula I, is that wherein Y is according to formula $-\text{CH}(\text{R}^5)\text{R}^6$. In another embodiment, the compound of formula I, is that of formula I, wherein Y is according to formula $-\text{CH}(\text{R}^5)-\text{W}-\text{R}^7$. In another embodiment, the compound of formula I, is that of formula I, wherein Y is according to formula $-\text{CH}(\text{R}^5)-\text{W}-\text{Rs}$. In another embodiment, the compound of formula I, is that of formula I, wherein R¹ and R² together with their ring carbons form a C₆- or C₁₀- aromatic fused ring which can be substituted by one or more halo, amino, alkyl, sulfonic acid, alkylsulfonyl or ω -alkylenesulfonic acid groups, or a C₁-C₃ alkylenedioxy group with the proviso that when Q is nitrogen R¹ and R² do not form a C₆ fused aromatic ring. In another embodiment, the compound of formula I, is that of the compound of formula I, wherein Q is S, and Y and Z are both -NH₂.

Further provided are compounds of formula II:



wherein (II)

wherein

- a. R¹ and R² are as set forth above;
- b. Y* is a group of the formula $-\text{CH}(\text{R}^5)-\text{R}^6$ wherein
 - (a) R⁵ is hydrogen, alkyl-, cycloalkyl-, alkenyl-, alkynyl-, aminoalkyl-, dialkylaminoalkyl-, (N-[C₆ or C₁₀]aryl)(N-alkyl)aminoalkyl-, piperidin-1-ylalkyl-, 1-pyrrolidinylalkyl, azetidinylalkyl, 4-alkylpiperazin-1-ylalkyl, 4-alkylpiperidin-1-ylalkyl, 4-[C₆ or C₁₀]arylpirazin-1-ylalkyl, 4-[C₆ or C₁₀]arylpiridin-1-ylalkyl, azetidin-1-ylalkyl, morpholin-4-ylalkyl,

PCT/US2007/223409

thiomorpholin-4-ylalkyl, piperidin-1-ylalkyl, [C₆ or C₁₀]aryl, or independently the same as R⁶ (in one embodiment, R⁵ is hydrogen or alkyl);

(b) R⁶ is

(1) cyano or R_T, wherein R_T is a C₆ or C₁₀ aryl (in one embodiment, cyano);

5 (2) a group of the formula -W-Rs, wherein W is -C(=O)- or -S(O)_n- where n=1 or 2, and Rs is a C₆ or C₁₀ aryl or a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur;

(3) a group of the formula -W-N(R⁹)R¹⁰, wherein

10 [a] R⁹ is hydrogen and R¹⁰ is an alkyl or cycloalkyl, optionally substituted by

(i) [C₆ or C₁₀]aryl, or

(ii) a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-

15 membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, said heteroaryl ring can be optionally substituted with one or more 1-pyrrolidinyl, 4-[C₆ or C₁₀]arylpirazin-1-yl, 4-[C₆ or C₁₀]arylpireridin-1-yl, azetidin-1-yl, and morpholin-4-yl, thiomorpholin-4-yl, piperidin-

20 1-yl, halo or (C₁-C₃)alkylenedioxy groups, or fused to a phenyl or pyridine ring, wherein the ring fusion is at a carbon-carbon double bond of the heteroaryl ring (in one embodiment, the optional substituents are one or more halo or (C₁-C₃)alkylenedioxy groups, or fused to a phenyl, which phenyl can be substituted with the general substitutions), or

25 (iii) a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or

[b] R⁹ is hydrogen or lower alkyl and R¹⁰ is Ar; or

30 [c] R⁹ is hydrogen or lower alkyl, and R¹⁰ is a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms are selected from the group consisting of oxygen, nitrogen and sulfur; or

100-3747-0001-0001

5 [d] R^9 and R^{10} are both alkyl groups; or

10 [e] R^9 and R^{10} together with N form a heterocycle containing 4-10 ring atoms which can incorporate up to one additional heteroatom selected from the group of N, O or S in the ring, wherein the heterocycle is optionally substituted with (C_6 -or C_{10})aryl, (C_6 -or C_{10})arylalkyl, or a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each such heteroaryl can be optionally substituted with one or more 1-pyrrolidinyl, 4-[C_6 or C_{10}]arylpiperazin-1-yl, 4-[C_6 or C_{10}]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C_1 - C_3)alkylenedioxy (in one embodiment, the optional substituents are one or more halo or (C_1 - C_3)alkylenedioxy); or

15 [f] R^9 and R^{10} are both hydrogen; and

g. X is a pharmaceutically acceptable anion, or

(B) a pharmaceutically acceptable salt of the compound, wherein aryl or Ar can be substituted with, in addition to any substitutions specifically noted, one or more of the Aryl General Substitutions or the Aryl Preferred General Substitutions;

20 wherein heterocycles, except those of Ar, can be substituted with, in addition to any substitutions specifically noted, the Heterocycle General Substitutions or the Heterocycle Preferred General Substitutions;

wherein the compound of formula II differs from a salt of 3-[2-(3,5-dimethoxyphenyl)-2-oxoethyl]-oxazolium by one or more of the lack or replacement of one of the methoxy substitutions, or the presence of one or more additional substitutions [preferably the differences in substitutions total two or more]; and

25 wherein the compound of formula II differs from a salt of 5-phenyl-3-phenylmethyl-oxazolium by one or more of the lack or replacement of the 5-phenyl substitution, or the presence of one or more additional substitutions [preferably the differences in substitutions total two or more].

Also provided are pharmaceutical formulations of compounds of formula II and a pharmaceutically acceptable excipient. The compounds of formula II are useful in the methods of the invention.

5-Phenyl-3-phenylmethyl-oxazolium chloride is described in Takamizawa et al.,

5 Chem. Pharm. Bull. 22(7): 1526-41, 1974, as an intermediate for synthesizing 1,4-oxazin-3-one and azetidin-2-one derivatives. 3-[2-(3,5-Dimethoxyphenyl)-2-oxoethyl]-oxazolium is described in J. Med. Chem. 32: 2301-6, 1989, as an inactive member of a series of compounds that sought to explore the glucose lowering effect of, particularly, certain imidazolium compounds.

10 In addition to the methods, compounds, and compositions thereof described herein, the invention provides methods or use in the treatments of the invention, or in the manufacture of a medicament for such therapeutic use.

Certain Fibrotic Diseases

15 Among the indications that can be treated with the invention are a number of indications linked to or associated with the formation of excess collagen. Among these, a number of the indications can be termed fibrotic diseases.

Such fibrotic diseases include systemic sclerosis, mixed connective tissue disease, fibrodysplasia, fibrocystic disease, sarcoidosis, myositis (e.g. polymyositis,

20 primary idiopathic polymyositis, childhood polymyositis, dermatomyositis, childhood dermatomyositis, primary idiopathic dermatomyositis in adults, inclusion body myositis, polymyositis or dermatomyositis associated with malignant tumors). Dermatomyositis can be associated with fibrosing or hypertrophic aspects, including fibrosing alveolitis and pulmonary fibrosis. Treatment using the invention is expected to treat, prevent,

25 reduce or ameliorate such diseases or hypertrophy, fibrotic hypertrophy or fibrosis in such diseases. Amelioration includes reducing the rate of progression of a disease.

30 Among these fibrotic diseases are diseases that have as a manifestation fibrotic vascular intimal hypertrophy. These diseases include vasculitis (including coronary artery vasculitis), polyarteritis nodosa or temporal arteritis. Treatment using the invention is expected to treat, prevent, reduce or ameliorate vascular intimal hypertrophy in such diseases.

These fibrotic diseases further include diseases that have as a manifestation fibrotic hypertrophy of skin and/or muscle tissue. These diseases include scleroderma,

eosinophilic fasciitis, discoid lesions associated with lupus or discoid lupus or surgical adhesions. Treatment using the invention is expected to treat, prevent, reduce or ameliorate such indications or hypertrophy or fibrosis of skin or muscle tissue.

Such fibrotic diseases further include diseases that have as a manifestation

5 fibrotic hypertrophy of nerve tissue. These diseases include cerebrosclerosis, annular sclerosis, diffuse sclerosis and lobar sclerosis. Treatment using the invention is expected to treat, prevent, reduce or ameliorate such diseases, or hypertrophy, fibrotic hypertrophy or fibrosis of nerve tissue in such diseases.

These fibrotic diseases further include fibrotic lung diseases that have as a

10 manifestation fibrotic hypertrophy or fibrosis of lung tissue. These diseases include pulmonary fibrosis (or interstitial lung disease or interstitial pulmonary fibrosis), idiopathic pulmonary fibrosis, the fibrotic element of pneumoconiosis (which is associated with exposure to environmental hazards such as smoking, asbestos, cotton lint, stone dust, mine dust and other particles), pulmonary sarcoidosis, fibrosing

15 alveolitis, the fibrotic or hypertrophic element of cystic fibrosis, chronic obstructive pulmonary disease, adult respiratory distress syndrome and emphysema. Treatment using the invention is expected to treat, prevent, reduce or ameliorate such diseases, or hypertrophy, fibrotic hypertrophy or fibrosis in such diseases.

Such fibrotic diseases further include diseases that have as a manifestation

20 fibrotic hypertrophy or fibrosis of prostate, liver, the pleura (e.g., pleurisy, pleural fibrosis) or pancreas. These diseases include benign prostatic hypertrophy (BPH) and fibrosis of the liver. Treatment using the invention is expected to treat, prevent, reduce or ameliorate such diseases, or hypertrophy, fibrotic hypertrophy or fibrosis in such diseases.

25 These fibrotic diseases further include diseases that have as a manifestation fibrotic hypertrophy or fibrosis of the bowel wall, such as inflammatory bowel disease, including Crohn's disease. Treatment using the invention is expected to treat, prevent, reduce or ameliorate such diseases, or hypertrophy, fibrotic hypertrophy or fibrosis in such diseases.

30

Arteriosclerosis, Atherosclerosis, Stiff Vessel Disease, Peripheral Vascular Disease, Coronary Heart Disease, Stroke, Myocardial Infarct, Cardiomyopathies, Restenosis

Arteriosclerosis is a disease marked by thickening, hardening, and loss of elasticity in arterial walls, of which atherosclerosis is a sub-type. Arteriosclerosis in turn falls within the genus of stiff vessel diseases. Without limitation to theory, it is believed that damage to the blood vessels of these diseases is due to AGE-caused damage, either 5 through protein cross-linking or the stimulation of bioactive agents, or both.

Accordingly, the first agents are used to treat, prevent, reduce or ameliorate stiff vessel disease, including arteriosclerosis and atherosclerosis. Peripheral vascular disease is an indication that overlaps with atherosclerosis but also covers disease which is believed to have a stronger inflammatory component. First agents are used to treat, prevent, reduce 10 or ameliorate peripheral vascular disease. Coronary heart disease is a form of atherosclerosis of the coronary arteries. First agents are used to treat, prevent, reduce or ameliorate coronary heart disease.

When the heart pumps blood into the vascular system, the ability of the arteries to expand helps to push blood through the body. When arteries become stiff, as they do in 15 the natural process of aging, the ability of the arteries to expand is diminished and also has consequences for the heart. The heart has to work harder to pump the blood into the stiff arteries, and eventually hypertrophies (enlarges in size) to accomplish this. A hypertrophied heart is an inefficient pump, and is one of the disorders that leads to congestive heart failure. One compound believed to work by a mechanism shared by the 20 compounds of the invention, 3-[2-phenyl-2-oxoethyl]-4,5-dimethyl-thiazolium salt, showed an ability to reverse the stiffness of arteries in a Phase IIa clinical trial, as measured by the ratio of stroke volume (ml) to pulse pressure (mm Hg). The potential clinical benefit of this is to lessen the effort that the heart must expend to push blood throughout the body. The effect is also believed to contribute to preventing hypertrophy 25 and subsequent inefficiency of the heart, which inefficiency would contribute to congestive heart failure.

Stroke is a cardiovascular disease that occurs when blood vessels supplying blood (oxygen and nutrients) to the brain burst or are obstructed by a blood clot or other particle. Nerve cells in the affected area of the brain die within minutes of oxygen 30 deprivation and loss of nerve cell function is followed by loss of corresponding bodily function. Of the four main types of stroke, two are caused by blood clots or other particles. The former two are the most common forms of stroke, accounting for about 70-80 percent of all strokes.

PCT/US2013/035007

Blood clots usually form in arteries damaged by atherosclerosis. When plaque tears from the sheer forces of blood flowing over an uneven, rigid cap atop the plaque site, thrombotic processes become involved at the "injury" site. As a result, clots can form. First agents are used to prevent, reduce or ameliorate the risk of stroke in patients 5 who have suffered previous strokes or have otherwise been identified as at risk.

First agents can also be used to treat, prevent, reduce or ameliorate peripheral vascular disease and periarticular rigidity.

Treatment with the first agents during the relatively immediate aftermath of a heart attack can be used to reduce the size of the myocardial infarct resulting from the 10 heart attack. This treatment is preferably administered within six hours of the heart attack, more preferably, within three hours. While the dosages discussed below can be used with this indication, such as a dose of 0.01 - 4.0 mg/kg administered orally or 0.01 - 2.0 mg/kg administered intravenously, preferably within the time period outlined above. Preferred routes of administration include i.v. injection or i.v. drip. Thereafter, optional 15 supplemental administrations can be made with the dosages described below.

Atherosclerosis is a disease that involves deposition of blood lipids in plaque in the arteries throughout the body. In coronary arteries, accumulation of plaque progressively leads to reduced coronary flow, with occlusion of the arteries causing focal death of cardiac tissue (myocardial infarction, heart attack). If the amount of tissue 20 that dies is large enough, death ensues. In a Phase IIa trial, one compound believed to work by a mechanism shared by the compounds of the invention, 3-[2-phenyl-2-oxoethyl]-4,5-dimethyl-thiazolium salt, increased the amount of circulating triglycerides (lipids). Consistent with the known presence of AGEs in plaque, the result indicates that the agent had a lipid mobilizing effect on arterial plaque. Reducing local deposits of 25 plaque should eventually lessen the risk of myocardial infarction and death due to heart attacks.

Fibrotic diseases further include diseases that have as a manifestation fibrotic hypertrophy of the heart. These diseases include endomyocardial fibrosis (wherein endocardium and subendocardium are fibrosed, such as in some manifestations of 30 restrictive cardiomyopathy), dilated congestive cardiomyopathy (a disorder of myocardial function with heart failure in which ventricular dilation and systolic dysfunction predominate), hypertrophic cardiomyopathy (characterized by marked ventricular hypertrophy with diastolic dysfunction in the absence of an afterload

TOP SECRET//COMINT

demand), and other cardio-hypertrophies. In dilated congestive cardiomyopathy, typically at presentation there is chronic myocardial fibrosis with diffuse loss of myocytes. In hypertrophic cardiomyopathy, usually the interventricular septum is hypertrophied more than the left ventricular posterior wall (asymmetric septal

5 hypertrophy). Treatment using the invention is expected to treat, prevent, reduce or ameliorate such diseases, or hypertrophy, fibrotic hypertrophy or fibrosis in such diseases.

Hypertrophies of the heart can be diagnosed and monitored by methods known in the art, such as by electrocardiogram, echocardiography or magnetic resonance imaging.

10 Such diagnostic methods can be applied in particular for subjects having a risk factor for such hypertrophy, such as congestive heart failure, prior cardiac surgery or diabetes. In one aspect, the invention comprises identifying cardio-hypertrophy with using biophysical diagnostic tools, and administering an active agent of the invention to treat, prevent, reduce or ameliorate such diseases, or hypertrophy, fibrotic hypertrophy or

15 fibrosis in such diseases. The invention can further include monitoring cardio-hypertrophy during the course of treatment with active agent.

Erosion or tearing of arterial wall plaque can occur due to the rough and irregular shape of the plaque as it forms from deposition of lipids and invasion of cells such as monocytes and macrophages (foam cells). When erosion occurs platelets and other

20 components of the blood clotting system are activated, resulting in formation of a clot (thrombus). When the thrombus grows to such a state that blood flow is reduced, severe angina attacks that characterize unstable angina can occur. Plaque forms irregular shapes and in doing so creates shear stresses from the flow of blood over this irregular form. It is the irregularity of plaque shape that leads to the dislodging or tearing of the plaque,

25 and to the subsequent invasion of reactive cells. On the surface of plaque is collagen, which is believed to contribute to the rigidity of the irregular shape. Without limitation to theory, it is believed that reducing the crosslinking of such a rigid collagen cap results in smoother blood flow, with a reduced risk of angina-causing tears. Accordingly, first agents are used to treat, prevent, reduce or ameliorate unstable angina.

30 Faithful conduction of the electrical impulse from the sinoatrial to the atrioventricular nodes depends upon close apposition of myocardial cells. Excess production of collagen in the heart, which occurs naturally with aging but more so in diabetes and in conditions of heart disorders such as hypertension, causes an increase in

40032747429410

the distance between myocardial cells, leading to atrial fibrillation. First agents are used to treat, prevent, reduce or ameliorate atrial fibrillation.

The fibrotic indications further include restenosis, which is the process of increasing artery closure following an operation to open the artery, such as balloon angioplasty.

Bladder Elasticity

Indications that can be treated, prevented, reduced or ameliorated with the first agents include loss of bladder elasticity. Bladder elasticity is tied to the frequency of urination, and the urgency of desire to urinate. Accordingly, the invention can be used to treat, prevent, reduce or ameliorate non-obstructive uropathy, a disorder characterized by an overactive bladder that entails increased frequency of urination, a strong and sudden desire to urinate (urgency) which may also be associated with involuntary urinary leakage (urge incontinence).

15

Macular Degeneration

The effect of the first agents in reducing levels of other endogenous bioactive agents, particularly VEGF and/or TGF[β], is believed to underlie effectiveness against macular degeneration or macular edema. Again, however, the invention is not limited to theory. Moreover, a anti-fibrotic effect or another effect against tissue hypertrophy may contribute. Treatment using the invention is expected to treat, prevent, reduce or ameliorate macular degeneration or macular edema. In one aspect of the invention, the treatment is used to treat, prevent, reduce or ameliorate the wet form of macular degeneration. In the wet form, new blood vessel growth has a greater contribution to the disease.

Amyotrophic lateral sclerosis (ALS)

ALS is associated with degradations of the motor neuron system and/or the posterior column of the spinal cord. In ALS patients, these structures tend to stain with AGE-reactive antibodies. Treatment using the invention is expected to treat, prevent, reduce or ameliorate ALS.

Rheumatoid Arthritis, Osteoarthritis, Bone Resorption

It is believed, without limitation to such theory, that reducing AGE accumulation at the joints affected by rheumatoid arthritis or osteoarthritis reduces stimulation of the production of cytokines involved in inflammatory processes of the disease. Treatment 5 using the invention is expected to treat, prevent, reduce or ameliorate rheumatoid arthritis or osteoarthritis. Similarly, it is believed that reducing AGE accumulation at bone reduces stimulation of bone resorption. Accordingly, the invention is used to treat, prevent, reduce or ameliorate osteoporosis, bone loss or brittle bone.

10 Dialysis

The first agents can be administered as part of a dialysis exchange fluid, thereby preventing, limiting or ameliorating the damage to tissue caused by the sugars found in such exchange fluid. For example, first agents are expected to prevent, limit or ameliorate the stiffening and sclerosing of peritoneal tissue that occurs in peritoneal 15 dialysis, as well as prevent, limit or ameliorate the formation of new blood vessels in the peritoneal membrane. In hemodialysis, first agents are expected to prevent, limit or ameliorate the stiffening and sclerosing of red blood cells and vasculature resulting from exposure to the sugars exchanged into the blood during dialysis. Exchange fluids for peritoneal dialysis typically contain 10 - 45 g/L of reducing sugar, typically 25 g/L, 20 which causes the formation of AGEs and consequent stiffening and degradation of peritoneal tissue. Similarly, hemodialysis fluids typically contain up to about 2.7 g/L of reducing sugar, typically 1 to 1.8 g/L. Thus, the invention provides methods by which the first agents are provided in these fluids and thereby prevent, limit or ameliorate the damage that would otherwise result. Alternatively, the invention provides methods 25 whereby the first agents are administered by the methods described below to prevent, limit or ameliorate such damage from dialysis. In hemodialysis, the exchange fluid preferably contains 0.006 - 2.3 mg/L of an agent of the invention, more preferably, 0.06 to 1.0 mg/L. In peritoneal dialysis, the exchange fluid preferably contains 0.01 to 24 mg/L of an agent of the invention, or preferably, 1.0 to 10 mg/L.

30 In one embodiment, preventing or ameliorating is effected with a second agent. A preferred route of administration is inclusion in the dialysis fluids. In hemodialysis, the exchange fluid preferably contains 0.125 to 2.5 mg/L of aminoguanidine, more preferably, 0.2 to 1.0 mg/L. In peritoneal dialysis, the exchange fluid preferably contains

1.25 to 25 mg/L of aminoguanidine, or preferably, 2.0 to 10 mg/L. In a preferred aspect of the invention, the first agents are initially administered, and subsequently second agents are used to moderate or limit damage thereafter.

5 **Asthma**

It is believed, without limitation to such theory, that the first agents or second agents act to prevent, reduce or ameliorate the small but significant thickening of the lung airways associated with asthma. Moreover, the agents are believed to reduce stimulation of the production of cytokines involved in inflammatory processes of the 10 disease. Accordingly, the agents are used to treat, prevent, reduce or ameliorate asthma. In this embodiment, one preferred route of administration is pulmonary, such as via an aerosol, though peroral administration is also preferred.

Carpal Tunnel Syndrome

15 It is believed, without limitation to such theory, that the first agents act to prevent, reduce or ameliorate fibrotic and cytokine-induced elements of carpal tunnel syndrome. Accordingly, the first agents are used to treat, prevent, reduce or ameliorate carpal tunnel syndrome.

20 Fibrotic diseases also include Dupuytren's contracture, a contracture of the palmar fascia often causing the ring and little fingers to bend into the palm. Treatment using the invention is expected to treat, prevent, reduce or ameliorate Dupuytren's contracture, or hypertrophy, fibrotic hypertrophy or fibrosis in Dupuytren's contracture.

In these embodiments, one preferred route of administration is local injection.

25 **Periodontal Disease**

The incidence of periodontal disease is higher in subjects with either insulin-deficient or insulin-resistant diabetes, with consequent hyperglycemia. Again, without limitation to such theory, it is believed that the first agents act to prevent, reduce or ameliorate AGE-induced cytokine action to create or exacerbate periodontal disease. 30 Accordingly, the first or second agents are used to treat, prevent, reduce or ameliorate periodontal disease. In this embodiment, one preferred primary or supplemental route of administration is via mouthwash, or compositions adapted for delivery into the subgingival periodontal pocket (such as implants and erodible microspheres). Peroral

administration is again useful. The mouthwash preferably contains 0.003 - 1.0 mg/L of a first agent, more preferably, 0.01 - 0.1 mg/L.

Sickle Cell Anemia

5 It is believed, without limitation to such theory, that the first agents act to prevent, reduce or ameliorate the restraint on blood flow caused by sickling. Again without limitation to theory, the mode of action is believed to be in reducing vascular as well as blood cell inelasticity. Accordingly, the first agents are used to treat, prevent, reduce or ameliorate a sickle cell anemia.

10

Erectile Dysfunction

Fibrotic diseases further include diseases that have as a manifestation fibrotic disease of the penis, including Peyronie's disease (fibrosis of the cavernous sheaths leading to contracture of the investing fascia of the corpora, resulting in a deviated and 15 painful erection). Treatment using the invention is expected to treat, prevent, reduce or ameliorate such diseases, or hypertrophy, fibrotic hypertrophy or fibrosis in such diseases.

Without limitation to theory, it is believed that the first agents act to prevent, reduce or ameliorate inelasticity of tissue of the penis and/or fibrosis of tissue of the 20 penis, such as inelasticity or fibrosis of the cavernous sheaths leading to contracture of the investing fascia of the corpora. At least partial restoration of the resulting inelasticity is believed to facilitate engorgement of the corpora cavernosa with blood. Accordingly, the first agents are used to treat, prevent, reduce or ameliorate erectile dysfunction.

25 **Limited Joint Mobility**

Limited Joint Mobility (LJM) is a disorder associated with diabetes and typically involves the joints of the hands. The fourth and fifth fingers are affected initially by limitation of motion. AGE glycation and crosslinking of tendons (collagen) in the joints is believed to contribute to the disease. It is believed, without limitation to theory, that 30 the first agents act to prevent, reduce or ameliorate inelasticity, fibrous tissue or cytokine-induced inflammation associated with limited joint mobility. Accordingly, the first agents are used to treat, prevent, reduce or ameliorate limited joint mobility.

4 0 6 2 5 4 4 1 0

Antineoplastic Applications

The first agents inhibit the stimulated formation of bioactive agents, such as VEGF, associated with angiogenesis. Angiogenesis is critical for both normal development and the growth and metastasis of solid tumors. Accordingly, the first 5 agents are used to treat, prevent, reduce or ameliorate the growth of neoplasms by limiting the formation of blood vessels needed to sustain the neoplasms.

End Stage Renal Disease, Diabetic Nephropathy

Diabetic Nephropathy is a complication of diabetes that evolves early, typically 10 before clinical diagnosis of diabetes is made. The earliest clinical evidence of nephropathy is the appearance of low but abnormal levels (>30 mg/day or 20 μ g/min) of albumin in the urine (microalbuminuria), followed by albuminuria (>300 mg/24 h or ~ 200 μ g/min) that develops over a period of 10–15 years. In patients with type 1 diabetes, diabetic hypertension typically becomes manifest early on, by the time that 15 patients develop microalbuminuria. Once overt nephropathy occurs, the glomerular filtration rate (GFR) falls over several years resulting in End Stage Renal Disease (ESRD) in 50% of type 1 diabetic individuals within 10 years and in $>75\%$ of type 1 diabetics by 20 years of onset of overt nephropathy. Albuminuria (i.e., proteinuria) is a marker of greatly increased cardiovascular morbidity and mortality for patients with 20 either type 1 or type 2 diabetes.

Without limitation to theory, it is believed that damage to the glomeruli and blood vessels of the kidney is due to AGE-caused damage, either through protein cross-linking or the stimulation of bioactive agents, or both. Accordingly, the first agents are used to treat, prevent, reduce or ameliorate damage to kidney in patients at risk for 25 ESRD. The first agents can also be used to treat, prevent, reduce or ameliorate glomerulosclerosis.

Hypertension, Isolated Systolic Hypertension

Cardiovascular risk correlates more closely with the systolic and the pulse 30 pressure than with the diastolic pressure. In diabetic patients, the cardiovascular risk profile of diabetic patients is strongly correlated to duration of diabetes, glycemic control and blood pressure. Structural matrix proteins contribute to the function of vessels and the heart, and changes in the physical behavior of cardiovascular walls are believed to be

important determinants of circulatory function. In elderly individuals, the loss of compliance in the aorta leads to isolated systolic hypertension, which in turn expands the arterial wall and thereby diminishes the dynamic range of elasticity. In vivo studies in rodents, canines and in primates indicate potential utility of 3-[2-phenyl-2-oxoethyl]-4,5-dimethyl-thiazolium salt in substantially ameliorating vascular stiffening. For example, in a dog model for diabetes, lower end diastolic pressure and increased end diastolic volume, indicators of ventricular elasticity, returned to a value at about the mid-point between the disease impaired value and the value for control dogs. Treatment with 3-[2-phenyl-2-oxoethyl]-4,5-dimethyl-thiazolium salt lead to a reduction in the mass of collagen in cardiovascular tissues. In situ hybridization studies demonstrate that 3-[2-phenyl-2-oxoethyl]-4,5-dimethyl-thiazolium salt reduces the expression of both Type IV collagen and TGFbeta.

Compared with that of a non-diabetic, the diabetic artery is smaller as it is stiffer. As in isolated systolic hypertension in which vessels stiffen with age and lose the dynamic range of expansion under systole. First agents are used to treat, prevent, reduce or ameliorate hypertension, including isolated systolic hypertension and diabetic hypertension. Moreover, the same benefit is anticipated for the more rare hypertensive disorder, pulmonary hypertension. Pulmonary hypertension is a rare blood vessel disorder of the lung in which the pressure in the pulmonary artery (the blood vessel that leads from the heart to the lungs) rises above normal levels and may become life threatening. The similarity in development of elevated blood pressure in the pulmonary bed with the increase in systemic blood pressure in diabetic hypertension and in isolated systolic hypertension suggests similar mechanisms are involved.

Pulse pressure is the difference between systolic and diastolic blood pressure. In a young human, systolic pressure is typically 120 mm Hg and diastolic pressure is 80 mm Hg, resulting in a pulse pressure of 40 mm Hg. With age, in many individuals pulse pressure increases, largely due to the increase in systolic pressure that results from stiff vessel disease. In individuals with pulse pressure greater than 60 mm Hg there is an increased risk of death from cardiovascular morbidities. In a Phase IIa trial, one compound believed to work by a mechanism shared by the compounds of the invention, 3-[2-phenyl-2-oxoethyl]-4,5-dimethyl-thiazolium salt, reduced pulse pressure in elderly patients with pulse pressures greater than 60 mm Hg in a statistically significant manner.

This decrease in pulse pressure was believed to be due primarily to the effect of the agent on lowering the systolic blood pressure.

The agents of the invention are used to treat, prevent, reduce or ameliorate reduced vascular compliance, elevated pulse pressure, and hypertension. Moreover, the 5 agents are used to reduce pulse pressure, increase vascular compliance, or decrease the risk of death.

Heart Failure

Congestive Heart Failure (CHF) is a clinical syndrome that entails cardiac disease 10 of the ventricle. Diastolic dysfunction is a subset of heart failure in which the left ventricle stiffens with age. The stiffening of the left ventricle that occurs in CHF and in diastolic dysfunction is believed to result from increased crosslinking of collagen fibers with age and/or fibrosis and related hypertrophy. First agents are used to treat, prevent, reduce or ameliorate heart failure.

15

Retinopathy

The effect of diabetes on the eye is called diabetic retinopathy and involves changes to the circulatory system of the retina. The earliest phase of the disease is known as background diabetic retinopathy wherein the arteries in the retina become 20 weakened and leak, forming small, dot-like hemorrhages. These leaking vessels often lead to swelling or edema in the retina and decreased vision. The next stage is proliferative diabetic retinopathy, in which circulation problems cause areas of the retina to become oxygen-deprived or ischemic. New vessels develop as the circulatory system attempts to maintain adequate oxygen levels within the retina. Unfortunately, these new 25 vessels hemorrhage easily. In the later phases of the disease, continued abnormal vessel growth and scar tissue may cause serious problems such as retinal detachment. First agents are used to treat, prevent, reduce or ameliorate diabetic retinopathy. The first agents can be administered by the methods described below, including by topical administration to the eye. The agents can also be administered by intravitreal implant.

30

DOCUMENT EVIDENCE

Cataracts, Other damage to Lens Proteins

AGE-mediated crosslinking and/or fibrotic processes are believed to contribute to cataract formation and formation of other damage to lens proteins. First agents are used to treat, prevent, reduce or ameliorate cataracts or other damage to lens proteins.

5

Alzheimer's Disease

Considerable evidence exists implicating AGEs that form in the neurofibrillary tangles (tau protein) and senile plaques (beta-amyloid peptide) in early neurotoxic processes of Alzheimer's disease. Insoluble human tau protein is likely crosslinked.

10 Glycation of insoluble tau from AD patients and experimentally AGE-modified tau generate oxygen free radicals, resulting in the activation of transcription via nuclear factor-kappa B, and resulting in an increase in amyloid beta-protein precursor and release of amyloid beta-peptides. Thus, A.G.E.-modified tau may function as an initiator in a positive feedback loop involving oxidative stress and cytokine gene expression. First
15 agents are used to treat, prevent, reduce or ameliorate Alzheimer's disease.

Other indications

For reasons analogous to those set forth above, the invention is believed to be useful in treating, preventing, reducing or ameliorating diabetes or its associated adverse
20 sequelae, and peripheral neuropathy. The agents, especially in topical form, increase elasticity and/or reduce wrinkles in skin. The agents further increase red blood cell deformability.

Combination Therapies

25 In cardiovascular therapies, first agents can be administered concurrently or in a combined formulation with one or more antioxidants. Examples of appropriate antioxidants are vitamin A, vitamin B6, vitamin C, vitamin E, glutathione, β -carotene, α -lipoic acid, coenzyme Q10, selenium and zinc, which are administered in effective amounts as is known in the art. Thus, the invention further provides pharmaceutical
30 compositions comprising an agent of the invention in combination with an effective amount of an antioxidant.

PCT/US2007/064460

In treating heart failure, cardiomyopathy or heart attack, first agents can be administered concurrently or in a combined formulation with one or more angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, calcium channel blockers, diuretics, digitalis or beta blockers. Examples of ACE inhibitors

5 include Captopril, Enalapril, Enalaprilat, Quinapril, Lisinopril and Ramipril, which are administered in effective amounts as is known in the art. Examples of angiotensin II receptor antagonists include Losartan, Irbesartan, Eprosartan, Valsartan and Candesartan, which are administered in effective amounts as is known in the art. Examples of calcium channel blockers include Amlodipine, Bepridil, Diltiazem, Felodipine, Isradipine,

10 Nicardipine, Nifedipine, Nimodipine and Verapamil, which are administered in effective amounts as is known in the art. Among diuretics, preferred examples include Furosemide, Bumetanide, Torsemide, Ethacrynic acid, Azosemide, Muzolimine, Piretanide, Tripamide and Hydrochlorothiazide, which are administered in effective amounts as is known in the art. Examples of beta adrenergic antagonists include

15 Metoprolol, Carvedilol, Bucindolol, Atenolol, Esmolol, Acebutolol, Propranolol, Nadolol, Timolol, Pindolol, Labetalol, Bopindolol, Carteolol, Penbutolol, Medroxalol, Levobunolol, Bisoprolol, Nebivolol, Celiprolol and Sotalol, which are administered in effective amounts as is known in the art. Thus, the invention further provides pharmaceutical compositions comprising an agent of the invention in combination with

20 an effective amount of an ACE inhibitor, diuretic, digitalis, beta blocker, or combination thereof.

For treating diabetes or complications thereof, the invention further provides pharmaceutical compositions comprising an agent of the invention in combination with an effective amount of a thiazolidinedione or "glitazone" diabetes drug, such as

25 Troglitazone, Rosiglitazone, and Pioglitazone.

In treating atherosclerosis, first agents can be administered concurrently or in a combined formulation with one or more statins (HMG CoA reductase inhibitors) or cholestyramine. Examples of statins include Mevastatin, Lovastatin, Simvastatin, Pravastatin and Fluvastatin, which are administered in effective amounts as is known in

30 the art. Thus, the invention further provides pharmaceutical compositions comprising an agent of the invention in combination with an effective amount of a statin, cholestyramine, or both.

For a number of indications discussed, including sickle cell anemia and diabetic complications, as well as wound healing and any other indication in which increased tissue perfusion is a useful means or adjunct to therapy, the first agents, or aminoguanidine or other agents of the aminoguanidine class can be administered with 5 erythropoietin, which is administered in effective amount as is known in the art. Erythropoietin includes stable forms of erythropoietin such as are marketed by Amgen (Thousand Oaks, CA).

For all indications, first agents can be administered concurrently or in a combined formulation with aminoguanidine or other agents of the aminoguanidine class, which are 10 administered in effective amounts as is known in the art.

The method of the invention is used to treat animals, preferably mammals, preferably humans.

In accordance with the present invention, methods for administering 15 pharmaceutical compositions containing certain compounds have been developed for treating the indications described. These agents are either substituted thiazolium, oxazolium, or imidazolium agents as shown in the Summary section above.

Pharmaceutical compositions of the invention include administering an effective amount of a compound of the formula I.

20 The alkyl, and alkenyl groups referred to below include both C1 to C6 linear and branched alkyl and alkenyl groups, unless otherwise noted. Alkoxy groups include linear or branched C1 to C6 alkoxy groups, unless otherwise noted.

“Ar” (consistent with the rules governing aromaticity) refers to a C₆ or C₁₀ aryl, or a 5 or 6 membered heteroaryl ring. The heteroaryl ring contains at least one and up to 25 three atoms of N for the 6 membered heteroaryl ring. The 5 membered heteroaryl ring contains; (1) from one to three atoms of N, or (2) one atom of O or S and zero to two atoms of N. The aryl or heteroaryl is optionally substituted as set forth below.

Nonlimiting examples of heteroaryl groups include: pyrrolyl, furanyl, thieryl, pyridyl, oxazolyl, pyrazolyl, pyrimidinyl, and pyridazinyl.

30 “Ar” can be fused to either a benzene, pyridine, pyrimidine, pyridazine, or (1,2,3) triazine ring.

“Rs” refers to a C₆ or C₁₀ aryl group (optionally substituted as set forth below) or a heterocycle containing 4-10 ring members and 1-3 heteroatoms selected from the group

consisting of oxygen, nitrogen and sulfur (wherein said heterocycle is optionally substituted as set forth below). Where Rs is a non aromatic heterocycle containing sulfur atom as ring members, the sulfur atoms can exist in various oxidation states, as $S(O)_n$, where n is 0,1, or 2.

5 As used herein, C_6 or C_{10} aryl groups and heterocycles containing 4 to 10 ring members are monocyclic or bicyclic. The ring fusions of the bicyclic heterocycles are at carbon-carbon bonds.

In certain embodiments of the invention, the thiazoliums, imidazoliums, and oxazoliums of the invention contain R^1 and R^2 substitutions that together with their ring 10 carbons (the C4-C5 carbons of the thiazoliums, imidazoliums, and oxazoliums) form a fused C5 to C7 cycloalkyl ring having up to two double bonds including the fused double bond (the C4-C5 double bond of the thiazoliums, imidazoliums, and oxazoliums). The cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxy carbonyl, amino, aminocarbonyl, carboxy, fluoro, and oxo substituents. One of 15 ordinary skill in the art will recognize that where cycloalkyl groups contain double bonds, the sp^2 hybridized carbon atoms can contain only one substituent (which can not be amino- or oxo-). sp^3 hybridized carbon atoms in the cycloalkyl ring can be geminally substituted with the exception that (1) two amino groups and (2) one amino and one fluoro group can not be substituted on the same sp^3 hybridized carbon atom.

20 In certain embodiments of the invention, the thiazoliums, imidazoliums, and oxazoliums of the invention contain R^1 and R^2 substitutions that together with their ring carbons (the C4-C5 carbons of the thiazoliums, imidazoliums, and oxazoliums) form a five to eight membered heterocycle (i.e. a bicyclic heterocycle is formed). In these 25 embodiments the heterocycle is preferably not aromatic. Particular compounds within these embodiments contain sulfur atoms in the ring fused to the thiazoliums, imidazoliums, and oxazoliums. These sulfur atoms in these particular compounds can exist in various oxidation states, as $S(O)_n$, where n is 0,1, or 2.

In certain embodiments of the invention, the thiazoliums, imidazoliums, and oxazoliums of the invention contain R^1 and R^2 substitutions that together with their ring 30 carbons (the C4-C5 carbons of the thiazoliums, imidazoliums, and oxazoliums) form a five or six membered heteroaryl ring (i.e., a bicyclic aromatic heterocycle is formed). A preferred bicyclic aromatic heterocycle of the invention is a purine analog [Q is N and R^1

and R² together with their ring carbons (the C4 and C5 of the imidazolium ring) form a pyrimidine ring].

In certain embodiments, the thiazoliums, imidazoliums, and oxazoliums of the invention contain a Y group which can be -CH(R⁵)-R⁶. In those embodiments where R⁵ is alkenyl, preferably alkenyl is -C=C-R^E, where R^E is alkyl, H, or hydroxy(C₁-C₆)alkyl. In those embodiments wherein R⁵ is alkynyl, preferably alkynyl is -C≡C-R^F, where R^F is alkyl, hydrogen, or hydroxy(C₁-C₆)alkyl.

Aryl or Ar, can generally be substituted with, in addition to any substitutions specifically noted one or more substituents selected from the group consisting of 10 acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C₁-C₃)alkylenedioxy, alkylsulfonyl [alkylS(O)₂-], alkylsulfinyl [alkylS(O)-], ω -alkylenesulfonic acid [-alkylSO₃H where n=1-6)], alkylthio, allyl, amino, ArC(O)-, ArO-, Ar-, Ar-alkyl-, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, trifluoromethyl, hydroxy, (C₂-C₆)hydroxyalkyl, 15 mercapto, nitro, sulfamoyl, sulfonic acid [-SO₃H], 1-pyrrolidinyl-, 4-[C₆ or C₁₀]arylpiperazin-1-yl-, 4-[C₆ or C₁₀]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, and piperidin-1-yl.

Heterocycles, except those of Ar, can generally be substituted with acylamino, alkanoyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, alkylsulfonyl 20 [alkylS(O)₂-], alkylsulfinyl [alkylS(O)-], alkylthio, amino, ArC(O)-, ArO-, Ar-, carboxy, dialkylamino, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, sulfamoyl, or trifluoromethyl. Preferably multiple substituents are located on different atoms of the heterocyclic ring, with the proviso that alkyl, alkylcarbonyl, and fluoro substituents can be substituted on the same carbon atom of the heterocyclic ring. Heterocycles can be 25 substituted with one or more substituents.

The halo atoms can be fluoro, chloro, bromo or iodo. Chloro and fluoro are preferred for aryl substitutions.

For the purposes of this invention, the compounds of formula (I) are formed as biologically or pharmaceutically acceptable salts. Useful salt forms include the halides 30 (particularly bromides and chlorides), tosylates, methanesulfonates, brosylates, fumarates, maleates, succinates, acetates, mesitylenesulfonates, and the like. Other

related salts can be formed using similarly non-toxic, and biologically or pharmaceutically acceptable anions.

Representative, non-limiting examples of compounds of the present invention are:

5 3-[2-(3-phenyl-5-isoxazolyl)-2-oxoethyl]thiazolium bromide
 3-[2-(3-phenyl-5-isoxazolyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide
 3-[2-(3-phenyl-5-isoxazolyl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide

10 3-[2-[4-(2-ethoxy-2-oxoethyl)-2-thiazolyl]amino-2-oxoethyl]-4,5-dimethylthiazolium chloride
 3-[2-(3-phenyl-5-isoxazolyl)-2-oxoethyl]-4-methyl-5-(6-hydroxyhexyl)thiazolium bromide

15 3-[2-(2,6-dimethyl-4-morpholinyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide
 3-(2-(1-piperidinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide
 3-(2-(2-furanyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide
 3-(2-(2-furanyl)-2-oxoethyl)-4-(2-hydroxypentyl)thiazolium bromide
 3-[2-(2-oxo-1,2,3,4-tetrahydro-6-quinolinyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide

20 3-(2-(1-pyrrolidinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide
 3-[2-(3-methyl-2-thianaphthetyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide
 3-[2-(4-phenyl-1-piperazinyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide
 3-(2-(2-thienyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide
 3-(2-(2-thienyl)-2-oxoethyl)-4-methyl-5-(2-hydroxyethyl)thiazolium bromide
 3-(2-(4-thiomorpholinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide

25 3-(2-(hexahydro-1-azepinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide
 3-[2-(4-[2-methoxyphenyl]-1-piperazinyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride
 3-(2-(octahydro-1-azocinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide
 3-(2-(2-pyridinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide

30 3-[2-(2-methyl-1-piperidinyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride
 3-[2-(2,6-dimethyl-1-piperidinyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride
 3-[2-(4-benzyl-1-piperidinyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride
 3-[2-(4-benzyl-1-piperazinyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride

3-[2-(3-phenyl-5-isoxazolyl)-2-oxoethyl]-4-octylthiazolium bromide
 3-(2-(4-morpholinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide
 3-[2-[4-(2-ethoxy-2-oxoethyl)-2-thiazolyl]amino-2-oxoethyl]-4,5-dimethylthiazolium chloride

5 3-(2-(4-morpholinyl)-2-oxoethyl)-4,5-dioctadecylthiazolium bromide
 3-[2-(2,6-dimethyl-4-morpholinyl)-2-oxoethyl]-4,5-dipentylthiazolium bromide
 3-(2-(1-piperidinyl)-2-oxoethyl)-4,5-didodecylthiazolium bromide
 3-(2-(2-furanyl)-2-oxoethyl)-5-decylthiazolium bromide
 3-[2-(2-oxo-1,2,3,4-tetrahydro-6-quinolinyl)-2-oxoethyl]-4,5-dioctylthiazolium

10 bromide
 3-(2-(1-pyrrolidinyl)-2-oxoethyl)-4,5-diethylthiazolium bromide
 3-[2-(3-methyl-2-thianaphthenyl)-2-oxoethyl]-4,5-dipentylthiazolium bromide
 3-[2-(4-phenyl-1-piperazinyl)-2-oxoethyl]thiazolium bromide
 3-(2-(2-thienyl)-2-oxoethyl)thiazolium bromide

15 3-(2-(2-thienyl)-2-oxoethyl)-4-methyl-5-(6-hydroxyhexyl)thiazolium bromide
 3-(2-(4-thiomorpholinyl)-2-oxoethyl)thiazolium bromide
 3-(2-(hexahydro-1-azepinyl)-2-oxoethyl)-4,5-dioctylthiazolium bromide
 3-(2-(octahydro-1-azocinyl)-2-oxoethyl)-4,5-didecylthiazolium bromide
 3-(2-(2-pyridinyl)-2-oxoethyl)-4,5-dioctylthiazolium bromide

20 3-[2-(2-methyl-1-piperidinyl)-2-oxoethyl]-4,5-dipropylthiazolium chloride
 3-[2-(2,6-dimethyl-1-piperidinyl)-2-oxoethyl]-4-methylthiazolium chloride
 3-[2-(4-benzyl-1-piperidinyl)-2-oxoethyl]-5-methylthiazolium chloride
 3-[2-(4-benzyl-1-piperazinyl)-2-oxoethyl]-4-octylthiazolium chloride
 3-aminothiazolium mesylenesulfonate;

25 3-amino-4,5-dimethylaminothiazolium mesylenesulfonate;
 2,3-diaminothiazolinium mesylenesulfonate;
 3-(2-methoxy-2-oxoethyl)thiazolium bromide;
 3-(2-methoxy-2-oxoethyl)-4,5-dimethylthiazolium bromide;
 3-(2-methoxy-2-oxoethyl)-4-methylthiazolium bromide;

30 3-(2-phenyl-2-oxoethyl)-4-methylthiazolium bromide;
 3-(2-phenyl-2-oxoethyl)-4,5-dimethylthiazolium bromide;
 3-amino-4-methylthiazolium mesylenesulfonate;
 3-(2-methoxy-2-oxoethyl)-5-methylthiazolium bromide;

3-(3-(2-phenyl-2-oxoethyl)-5-methylthiazolium bromide;
3-[2-(4-bromophenyl)-2-oxoethyl] thiazolium bromide;
3-[2-(4-bromophenyl)-2-oxoethyl]-4-methylthiazolium bromide;
3-[2-(4-bromophenyl)-2-oxoethyl]-5-methylthiazolium bromide;
5 3-[2-(4-bromophenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;
3-(2-methoxy-2-oxoethyl)-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;
3-(2-phenyl-2-oxoethyl)-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;
3-[2-(4-bromophenyl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium
bromide;

10 3,4-dimethyl-5-(2-hydroxyethyl)thiazolium iodide;
3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide;
3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride;
3-(2-methoxy-2-oxoethyl)benzothiazolium bromide;
3-(2-phenyl-2-oxoethyl)benzothiazolium bromide;

15 3-[2-(4'-bromophenyl)-2-oxoethyl]benzothiazolium bromide;
3-(carboxymethyl)benzothiazolium bromide;
2,3-(diamino)benzothiazolium mesitylenesulfonate;
3-(2-amino-2-oxoethyl)thiazolium bromide;
3-(2-amino-2-oxoethyl)-4-methylthiazolium bromide;

20 3-(2-amino-2-oxoethyl)-5-methylthiazolium bromide;
3-(2-amino-2-oxoethyl)-4,5-dimethylthiazolium bromide;
3-(2-amino-2-oxoethyl)benzothiazolium bromide;
3-(2-amino-2-oxoethyl)-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;
3-amino-5-(2-hydroxyethyl)-4-methylthiazolium mesitylenesulfonate;

25 3-(2-methyl-2-oxoethyl)thiazolium chloride;
3-amino-4-methyl-5-(2-acetoxyethyl)thiazolium mesitylenesulfonate;
3-(2-phenyl-2-oxoethyl)thiazolium bromide;
3-(2-methoxy-2-oxoethyl)-4-methyl-5-(2-acetoxyethyl)thiazolium bromide;
3-(2-amino-2-oxoethyl)-4-methyl-5-(2-acetoxyethyl)thiazolium bromide;

30 2-amino-3-(2-methoxy-2-oxoethyl)thiazolium bromide;
2-amino-3-(2-methoxy-2-oxoethyl)benzothiazolium bromide;
2-amino-3-(2-amino-2-oxoethyl)thiazolium bromide;
2-amino-3-(2-amino-2-oxoethyl) benzothiazolium bromide;

3-[2-(4-methoxyphenyl)-2-oxoethyl]thiazolium bromide;
3-[2-(2,4-dimethoxyphenyl)-2-oxoethyl]thiazolium bromide;
3-[2-(4-fluorophenyl)-2-oxoethyl]thiazolium bromide;
3-[2-(2,4-difluorophenyl)-2-oxoethyl]thiazolium bromide;
5 3-[2-(4-diethylaminophenyl)-2-oxoethyl]thiazolium bromide;
3-propargylthiazolium bromide;
3-propargyl-4-methylthiazolium bromide;
3-propargyl-5-methylthiazolium bromide;
3-propargyl-4,5-dimethylthiazolium bromide;
10 3-propargyl-4-methyl-5-(2-hydroxyethyl)-thiazolium bromide;
3-(2-[3-methoxyphenyl]-2-oxoethyl)thiazolium bromide;
3-(2-[3-methoxyphenyl]-2-oxoethyl)-4-methyl-5-(2-hydroxyethyl)thiazolium
bromide;
3-(2-[3-methoxyphenyl]-2-oxoethyl)-benzothiazolium bromide;
15 2,3-diamino-4-chlorobenzothiazolium mesylenesulfonate;
2,3-diamino-4-methylthiazolium mesylenesulfonate;
3-amino-4-methyl-5-vinylthiazolium mesylenesulfonate;
2,3-diamino-6-chlorobenzothiazolium
2,6-diamino-benzothiazole dihydrochloride;
20 2,6-diamino-3-[2-(4-methoxyphenyl)-2-oxoethyl]benzothiazolium bromide;
2,6-diamino-3-[2-(3-methoxyphenyl)-2-oxoethyl]benzothiazolium bromide;
2,6-diamino-3-[2-(4-diethylaminophenyl)-2-oxoethyl]benzothiazolium bromide;
2,6-diamino-3-(2-(4-bromophenyl)-2-oxoethyl)benzothiazolium bromide;
2,6-diamino-3-[2-(2-phenyl)-2-oxoethyl]benzothiazolium bromide;
25 2,6-diamino-3-[2-(4-fluorophenyl)-2-oxoethyl]benzothiazolium bromide;
3-acetamido-4-methyl-5-thiazolyl-ethyl acetate mesylenesulfonate;
2,3-diamino-5-methylthiazolium mesylenesulfonate;
3-[2-(2-naphthyl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)-thiazolium bromide;
3-[2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-oxoethyl]-4-methyl-5-(2-
30 hydroxyethyl)thiazolium bromide;
3-[2-(2,6-dichlorophenethylamino)-2-oxoethyl]-4-methyl-5-(2-
hydroxyethyl)thiazolium bromide;
3-[2-dibutylamino-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;

3-[2-(4-carbethoxyanilino)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;

3-(2-(2,6-diisopropylanilino)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;

5 3-amino-4-methyl-5-[2-(2,6-dichlorobenzyl)ethoxy]thiazolium
mesitylenesulfonate;

3-[2-(4-carbmethoxy-3-hydroxyanilino)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;

2,3-diamino-4,5-dimethylthiazolium mesitylene sulfonate;

10 2,3-diamino-4-methyl-5-(2-hydroxyethyl)thiazolium mesitylene sulfonate;

2,3-diamino-5-(3,4-trimethylenedioxy phenyl)-thiazolium mesitylene sulfonate;

3-[2-(1,4-benzodioxan-6-yl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;

3-[2-(3,4-trimethylenedioxyphenyl)-2-oxoethyl]-4-methyl-5-(2-

15 hydroxyethyl)thiazolium bromide;

3-(2-[3,4-benzodioxan-6-yl]-2-oxoethyl)thiazolium bromide;

3-[2-(3,4-trimethylenedioxyphenyl)-2-oxoethyl]thiazolium bromide;

3-[2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-oxoethyl]thiazolium bromide;

3-[2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-oxoethyl]-4-methylthiazolium

20 bromide;

3-[2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-oxoethyl]-5-methylthiazolium bromide;

3-[2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

25 3-[2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-oxoethyl]-benzothiazolium bromide;
1-methyl-3-[2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-oxoethyl]imidazolium
bromide;

3-[2-(4-*n*-pentylphenyl)-2-oxoethyl]thiazolium bromide;

3-[2-(4-*n*-pentylphenyl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium

30 bromide;

3-[2-(4-diethylaminophenyl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;

3-(2-phenyl-2-oxoethyl)-4-methyl-5-vinylthiazolium bromide;

3-[2-(3,5-tert-butyl-4-hydroxyphenyl)-2-oxoethyl]-4-methyl-5-vinylthiazolium bromide;

3-(2-tert-butyl-2-oxoethyl)thiazolium bromide

3-(2-tert-butyl-2-oxoethyl)-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;

5 3-(3'-methoxybenzyl)-4-methyl-5-(2-hydroxyethyl)thiazolium chloride;

3-(2,6-dichlorobenzyl)-4-methyl-5-(2-hydroxyethyl)thiazolium chloride;

3-(2-nitrobenzyl)-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;

3[2-(4-chlorophenyl)-2-oxoethyl]thiazolium bromide;

3[2-(4-chlorophenyl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium

10 bromide

3[2-(4-methoxyphenyl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide.

3-[2-(3-phenyl-5-isoxazolyl)-2-oxoethyl]thiazolium bromide

3-[2-(3-phenyl-5-isoxazolyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide

15 3-[2-(3-phenyl-5-isoxazolyl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide

3-[2-[4-(2-ethoxy-2-oxoethyl)-2-thiazolyl]amino-2-oxoethyl]-4,5-dimethylthiazolium chloride

3-[2-(3-phenyl-5-isoxazolyl)-2-oxoethyl]-4-methyl-5-(6-

20 hydroxyhexyl)thiazolium bromide

3-[2-(2,6-dimethyl-4-morpholinyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide

3-(2-(1-piperidinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide

3-(2-(2-furanyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide

3-(2-(2-furanyl)-2-oxoethyl)-4-(2-hydroxypentyl)thiazolium bromide

25 3-[2-(2-oxo-1,2,3,4-tetrahydro-6-quinolinyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide

3-(2-(1-pyrrolidinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide

3-[2-(3-methyl-2-thianaphthetyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide

3-[2-(4-phenyl-1-piperazinyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide

30 3-(2-(2-thienyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide

3-(2-(2-thienyl)-2-oxoethyl)-4-methyl-5-hydroxyethylthiazolium bromide

3-(2-(4-thiomorpholinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide

3-(2-(hexahydro-1-azepinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide

RECORDED

3-[2-(4-[2-methoxyphenyl]-1-piperazinyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride

3-(2-(octahydro-1-azocinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide

3-(2-(2-pyridinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide

5 3-[2-(2-methyl-1-piperidinyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride

3-[2-(2,6-dimethyl-1-piperidinyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride

3-[2-(4-benzyl-1-piperidinyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride

3-[2-(4-benzyl-1-piperazinyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride

3-[2-(3-phenyl-5-isoxazolyl)-2-oxoethyl]-4-octylthiazolium bromide

10 3-(2-(4-morpholinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide

3-[2-[4-(2-ethoxy-2-oxoethyl)-2-thiazolyl]amino-2-oxoethyl]-4,5-dipropylthiazolium chloride

3-(2-(4-morpholinyl)-2-oxoethyl)-4,5-dioctadecylthiazolium bromide

3-[2-(2,6-dimethyl-4-morpholinyl)-2-oxoethyl]-4,5-dipentylthiazolium bromide

15 3-(2-(1-piperidinyl)-2-oxoethyl)-4,5-didodecylthiazolium bromide

3-(2-(2-furanyl)-2-oxoethyl)-5-decylthiazolium bromide

3-[2-(2-oxo-1,2,3,4-tetrahydro-6-quinolinyl)-2-oxoethyl]-4,5-dioctylthiazolium bromide

3-(2-(1-pyrrolidinyl)-2-oxoethyl)-4,5-diethylthiazolium bromide

20 3-[2-(3-methyl-2-thianaphthetyl)-2-oxoethyl]-4,5-dipentylthiazolium bromide

3-[2-(4-phenyl-1-piperazinyl)-2-oxoethyl]thiazolium bromide

3-(2-(2-thienyl)-2-oxoethyl)thiazolium bromide

3-(2-(2-thienyl)-2-oxoethyl)-4-methyl-5-(6-hydroxyhexyl)thiazolium bromide

3-(2-(4-thiomorpholinyl)-2-oxoethyl)thiazolium bromide

25 3-(2-(hexahydro-1-azepinyl)-2-oxoethyl)-4,5-dioctylthiazolium bromide

3-(2-(octahydro-1-azocinyl)-2-oxoethyl)-4,5-didecylthiazolium bromide

3-(2-(2-pyridinyl)-2-oxoethyl)-4,5-dioctylthiazolium bromide

3-[2-(2-methyl-1-piperidinyl)-2-oxoethyl]-4,5-dipropylthiazolium chloride

3-[2-(2,6-dimethyl-1-piperidinyl)-2-oxoethyl]-4-methylthiazolium chloride

30 3-[2-(4-benzyl-1-piperidinyl)-2-oxoethyl]-5-methylthiazolium chloride

3-[2-(4-benzyl-1-piperazinyl)-2-oxoethyl]-4-octylthiazolium chloride

1-methyl-3-[2-(3-methoxyphenyl)-2-oxoethyl]imidazolium bromide;

1-methyl-3-[2-(4-methoxyphenyl)-2-oxoethyl]imidazolium bromide;

1-methyl-3-[2-(2,4-dimethoxyphenyl)-2-oxoethyl]imidazolium bromide;
1-methyl-3-[2-(4-diethylaminophenyl)-2-oxoethyl]imidazolium bromide;
1-methyl-3-[2-amino-2-oxoethyl]imidazolium bromide;
1-methyl-2-amino-imidazolium mesitylene sulfonate;

5 1-methyl-3-[2-phenyl-2-oxoethyl]imidazolium bromide;
3-amino-1-(ethoxycarbonylpentyl)imidazolium mesitylenesulfonate;
1-(ethoxycarbonylpentyl)-3-[2-(3-methoxyphenyl)-2-oxoethyl]imidazolium bromide;

10 1-methyl-3-[2-(4-bromophenyl)-2-oxoethyl]imidazolium bromide;
1-methyl-3-[2-(4-fluorophenyl)-2-oxoethyl]imidazolium bromide;
1-methyl-3-[2-(3,4-difluorophenyl)-2-oxoethyl]imidazolium bromide;
1-(ethoxycarbonylpentyl)-3-[2-(4-methoxyphenyl)-2-oxoethyl]imidazolium bromide;

15 1-(4-acetylphenyl)-3-amino-imidazolium mesitylenesulfonate;
1-(ethoxycarbonylpentyl)-3-[2-(4-methoxyphenyl)-2-oxoethyl]imidazolium bromide;
1-(ethoxycarbonylpentyl)-3-[2-(4-methylphenyl)-2-oxoethyl]imidazolium bromide;

20 1-amino-3-benzoyl-imidazolium mesitylene sulfonate;
1-methyl-3-(2-naphth-2-yl-2-oxoethyl)imidazolium bromide;
1-methyl-3-[(4-biphen-1-yl)-2-oxoethyl]imidazolium bromide;
1-methyl-3-[(3-trifluoromethylphenyl)-2-oxoethyl]imidazolium bromide;
1-methyl-3-[4-(2,4-difluorophenyl)-2-oxoethyl]imidazolium chloride;
3-[2-(thien-2-yl)-2-oxoethyl]-1-methyl-5-imidazolium bromide;

25 1-methyl-3-[2-(2,4,6-trimethylphenyl)-2-oxoethyl]imidazolium bromide;
1-methyl-3-[2-(2,4-dichlorophenyl)-2-oxoethyl]imidazolium chloride;
3-(2-phenyl-2-oxoethyl)-1-phenylimidazolium chloride;
3-(2-phenyl-2-oxoethyl)-1-ethylimidazolium chloride;
3-(2-phenyl-2-oxoethyl)-1-butylimidazolium chloride;

30 3-(2-phenyl-2-oxoethyl)-1-allylimidazolium chloride;
3-(2-trifluoromethylphenyl-2-oxoethyl)-4,5-dimethylthiazolium bromide;
3-(2-trifluoromethylphenyl-2-oxoethyl)-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;

3-(2-trifluoromethylphenyl-2-oxoethyl)-1-methylimidazolium bromide;
3-(2-trifluoromethylphenyl-2-oxoethyl)-1-methylimidazolium bromide;
1-butyl-3-amino-imidazolium-mesitylenesulfonate;
3-[2-(thien-2-yl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;
5 3-[2-(pyrrolidin-1-yl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;
3-(2-phenyl-2-oxoethyl)-1,2-dimethylimidazolium chloride;
3-amino-1,2-dimethylimidazolium mesitylenesulfonate;
3-[2-(pyrrolidin-1-yl)-2-oxoethyl]-1-ethylimidazolium chloride;
3-[2-(pyrrolidin-1-yl)-2-oxoethyl]-1-phenylimidazolium chloride;
10 3-[2-(pyrrolidin-1-yl)-2-oxoethyl]-1-methylimidazolium chloride;
3-[2-(thien-2-yl)-2-oxoethyl]-1-ethylimidazolium bromide;
3-[2-(thien-2-yl)-2-oxoethyl]-1-phenylimidazolium bromide;
3-[2-(thien-2-yl-2-oxoethyl]-1,4,5-trimethylimidazolium bromide;
15 3-[2-(pyrrolidin-2-yl)-2-oxoethyl]-1,4,5-trimethylimidazolium chloride;
3-[2-(4-chlorophenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;
3-[2-(4-bromophenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;
3-[2-(4-fluorophenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;
3-[2-(2,4-difluorophenyl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;
3-[2-(2,4-dichlorophenyl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;
20 3-[2-(3,4-difluorophenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;
3-[2-(2-methoxyphenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;
3-[2-(3-methoxyphenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;
3-[2-(4-methoxyphenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;
3-[2-(2,4-dimethoxyphenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;
25 3-[2-(2,5-dimethoxyphenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;
3-[2-(2,4,6-trimethylphenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;
3-[2-(4-methylphenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;
3-[2-(4-diethylaminophenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;
3-[2-amino-2-oxoethyl]-1,2-dimethylimidazolium bromide;
30 3-[2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-oxoethyl]-1,2-dimethyl-imidazolium bromide;
3-[2-(3,4-trimethylenedioxyphenyl)-2-oxoethyl]-1,2-dimethyl-imidazolium bromide;

3-[2-(4-biphenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;

3-[2-(3,5-dichloroanilino)-2-oxoethyl]-1,2-dimethylimidazolium bromide;

3-[2-(4-trifluoromethylphenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;

3-[2-(2,6-dichlorophenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;

5 3-[2-(thiomorpholin-4-yl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[2-(morpholin-4-yl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[2-(piperidin-1-yl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[2-hexamethyleneimino-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[2-heptamethyleneimino-2-oxoethyl]-1,2-dimethylimidazolium chloride;

10 3-[2-naphthyl-2-oxoethyl]-1,2-dimethylimidazolium bromide;

3-[2-(2-trifluoromethylphenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;

3-[2-(2-trifluoromethylphenyl)-2-oxoethyl]-2,4,5-trimethylthiazolium bromide;

3-(2-methyl-2-oxoethyl)-1,2-dimethylimidazolium chloride;

3-(2-phenyl-2-oxoethyl)-2-amino-1-methylbenzimidazolium chloride;

15 3-[2-(thiomorpholin-4-yl)-2-oxoethyl]-1-methylimidazolium chloride;

3-[2-(4-phenylpiperazin-1-yl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[2-(4-benzylpiperazin-1-yl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[2-{6-(1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-naphthalyl)}-2-oxoethyl]-1,2-dimethylimidazolium bromide;

20 3-[2-(1,4-benzodioxan-6-yl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;

3-[2-(phenyl)-2-oxoethyl]-5-chloro-3-methyl-1-ethylimidazolium chloride;

3-[2-(phenyl)-2-oxoethyl]-4-methyl-2-ethylthiazolium chloride;

3-(2-phenyl-2-oxoethyl)-1-methyl-2-aminoimidazolium chloride;

3-[2-(pyrrolidin-2-yl)-2-oxoethyl]-2-amino-1-methylimidazolium chloride;

25 3-(2-phenyl-2-oxoethyl)-1,2-dimethyl-5-nitroimidazolium chloride;

3-[2-(4-acetylanilino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[2-(4-carboethoxyanilino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[2-(2,6-diisopropylanilino)-2-oxoethyl]-1,2-dimethylimidazolium bromide;

3-[2-anilino-2-oxoethyl]-1,2-dimethylimidazolium chloride;

30 3-[(4-bromoanilino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[2-(4-[morpholin-4-yl]phenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;

3-[2-dibutylamino-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[2-(2,6-dichloro-phenethylamino)-2-oxoethyl]-1,2-dimethylimidazolium;

3-[2-(3-hydroxy-4-methoxycarbonylanilino)-2-oxoethyl]-1,2-dimethylimidazolium bromide;

3-[2-cyclopentylamino-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[2-neopentylamino-2-oxoethyl]-1,2-dimethylimidazolium chloride;

5 3-[2-(pyridin-2-yl)-2-oxoethyl]-4,5-dimethylimidazolium bromide;

3-(2-phenyl-2-oxoethyl)-1,4,5-trimethylimidazolium chloride;

3-(2-phenyl-2-oxoethyl)-1,2,4,5-tetramethylimidazolium chloride;

3-[2-(6-[1,2,3,4-tetrahydroquinolinyl])-2-oxoethyl]-1,2-dimethylimidazolium chloride;

10 3-[2-(2,6-difluorophenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;

1-vinyl-3-[2-phenyl-2-oxoethyl]imidazolium chloride;

1-(4-hydroxyphenyl)-3-(2-phenyl-2-oxoethyl)imidazolium chloride;

1-(4-acetylphenyl)-3-(2-phenyl-2-oxoethyl)imidazolium chloride;

1-methyl-3-(2-phenyl-2-oxoethyl)benzimidazolium chloride;

15 1,5-dicyclohexyl-3-(2-phenyl-2-oxoethyl)imidazolium chloride;

1-(4-methoxycarbonylphenyl)-3-(2-phenyl-2-oxoethyl)imidazolium chloride;

1-benzyl-3-(2-phenyl-2-oxoethyl)imidazolium chloride;

1-(4-methoxyphenyl)-3-(2-phenyl-2-oxoethyl)imidazolium chloride;

3-[2-(tert-butylamino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

20 3-[2-(2,4-difluoroanilino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[2-(2,4,6-trimethylanilino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-(2-cyclohexylamino-2-oxoethyl)-1,2-dimethylimidazolium chloride;

3-[2-(4-carboxy-3'-hydroxyanilino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

25 3-[2-([2-morpholin-4-yl]ethylamino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[2-(3-[2-methylpiperidin-1-yl]propylamino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-(2-veratrylamino-2-oxoethyl)-1,2-dimethylimidazolium chloride;

30 3-[2-(thiazolidin-3-yl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[2-(1-adamantanamino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[2-(2-adamantanamino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[2-(2-indanylamino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[2-(2'-[3"-chlorobenzoyl]-5-chloroanilino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[2-(4-ethoxycarbonylthiazol-2-yl)amino-2-oxoethyl]-1,2-dimethylimidazolium chloride;

5 3-(cyclohexylamino-2-oxoethyl)-2,4,5-trimethylthiazolium chloride;
3-[2-(2-chloroanilino)-2-oxoethyl]-1,2-dimethylimidazolium bromide;
3-[2-(2-chloroanilino)-2-oxoethyl]-2,4,5-trimethylthiazolium bromide;
3-[2-(3,4-dimethoxyphenethylamino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

10 3-[2-(2,4-dichloroanilino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;
3-[2-(2,6-dichloroanilino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;
3-[(2-pyrrolidin-1-yl)-2-oxoethyl]-1,2,4,5-tetramethylimidazolium chloride;
3-[2-(4-[pyrrolidin-1-yl]piperidin-1-yl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

15 3-[2-(4-[piperidin-1-yl]piperidin-1-yl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;
3-[2-(2,6-difluoroanilino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;
3-(2-cyclobutylamino-2-oxoethyl)-1,2-dimethylimidazolium chloride;
3-[2-(3,5-difluoroanilino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

20 3-[2-(2-fluoroanilino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;
3-[2-(1R,2R,3R,5S-isopinocampheylamino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;
3-[2-(1,3,3-trimethyl-6-azabicyclo[3.2.1]octanyl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

25 3-[2-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;
3-[2-(1,2,3,4-tetrahydro-1-naphthylamino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

30 1-(4-methoxyphenyl)-3-aminoimidazolium mesitylenesulfonate;
1-benzyl-3-aminoimidazolium mesitylenesulfonate;
1-vinyl-3-aminoimidazolium mesitylenesulfonate;
1-methyl-3-aminoimidazolium mesitylenesulfonate;
1-(4-methoxycarbonylphenyl)-3-aminoimidazolium mesitylenesulfonate;

九月九日

3-(2-phenyl-2-hydroxyethyl)-4,5-dimethylthiazolium;
S(-) 3-(2-Phenyl-2-hydroxyethyl)-4,5-dimethylthiazolium chloride;
R(-) 3-(2-Phenyl-2-hydroxyethyl)-4,5-dimethylthiazolium chloride;
3-[2-(2-Hydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;
5 3-[2-(3-Hydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;
3-[2-(4-Hydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;
3-(2-phenyl-2-oxoethyl)-4-methyl-5-(hydroxymethyl)-thiazolium chloride;
3-[2-(2,4-dihydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;
3-[2-(3,5-dihydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;
10 3-[2-(2,5-dihydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;
3-[2-(3,4-dihydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride;
3-[2-(2',3'-dihydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium;
thiamine hydrochloride;
(1-ethyl-hexanoate)-3-[2-(4-chlorophenyl)-2-oxoethyl]imidazolium bromide;
15 3-[2-[6-[1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-naphthalyl]]-2-
oxoethyl]thiazolium bromide;
3-[2-(3,5-dichloroanilino)-2-oxoethyl]thiazolium bromide;
3-[2-(4-biphenyl)-2-oxoethyl]thiazolium bromide;
Cocarboxylase (diphosphate ester of thiamine HCl);
20 monophosphate ester of thiamine HCl;
3-[2-(9H-fluoren-2-yl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;
3-[2-{6-(1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-naphthalyl)}-2-oxoethyl]-4,5-
dimethylthiazolium bromide;
3-[2-{5-(3-phenylisoxazolyl)}-2-oxoethyl]-4,5-dimethylthiazolium bromide;
25 3-[2-(4-biphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;
3-[2-(3,5-dichloroanilino)-2-oxoethyl]-4,5-dimethylthiazolium bromide;
3-[2-{6-[1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-naphthalyl]}-2-oxoethyl]-4-
methyl-5-(2-hydroxyethyl)thiazolium bromide;
3-[2-(3-phenylisoxazol-5-yl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium
30 bromide;
3-[2-(4-biphenyl)-2-oxoethyl]-4-methyl-5-(2'-hydroxyethyl)thiazolium bromide;
3-[2-(3,5-dichloroanilino)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium
bromide;

3-{{2-(3-methoxybenzoyl)amino}benzyl}-4,5-dimethylthiazolium bromide;

3-[2-(2-amino-5-carboethoxymethylene-thiazoly)-2-oxoethyl]-4,5-dimethylthiazolium chloride;

3-[2-(morpholin-4-yl-2-oxoethyl]-4,5-dimethylthiazolium bromide;

5 3-[2-(2,6-dimethylmorpholin-4-yl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-(piperidin-1-yl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-(fur-2-yl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-[6-(2-oxo-1,2,3,4-tetrahydroquinolinyl)]-2-oxoethyl]-4,5-dimethylthiazolium bromide;

10 3-[2-(pyrrolidin-1-yl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-(4-carboxyanilino)-2-oxoethyl]-4,5-dimethylthiazolium chloride;

3-[2-(2-{3-methylbenzo[b]thienyl})-2-oxoethyl]-4,5-dimethylthiazolium bromide;

15 3-[2-(4-phenylpiperazin-1-yl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-(4-fluorophenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-(4-methoxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-(4-trifluoromethyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-(2,4-difluorophenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-(2,4,6-trimethylphenyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride;

20 3-[2-tert-butyi-2-oxoethyl]-4,5-dimethylthiazolium chloride;

3-[2-(2,4-dichlorophenyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride;

3-[2-(4-Diethylaminophenyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride;

3-(2-methyl-2-oxoethyl)-4,5-dimethylthiazolium chloride;

3-[2-(2,6-dichlorophenyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride;

25 3-(2-phenyl-2-oxoethyl)-4-phenylthiazolium chloride;

3-[2-(2,4-dichlorophenyl)-2-oxoethyl]-4-phenylthiazolium chloride;

3-[2-(2,4,6-trimethylphenyl)-2-oxoethyl]-4-phenylthiazolium bromide;

3-(2-methyl-2-oxoethyl)-4-methyl-5-(hydroxyethyl) thiazolium chloride;

3-[2-(2,4-dichlorophenyl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium;

30 3-[2-(2,4,6-trimethylphenyl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium chloride;

3-(1-methyl-2-phenyl-2-oxoethyl)-4,5-dimethylthiazolium chloride;

3-(phenylthiomethyl)-4,5-dimethylthiazolium chloride;

3-[2-(thien-2-yl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;
 3-[2-(2-thien-2-yl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;
 3-[2-phenyl-2-oxoethyl]-4,5-cyclohexenyl-thiazolium bromide;
 3-[2-(2,4-dichlorophenyl)-2-oxoethyl]-4,5-cyclohexeno-thiazolium chloride;
 5 3-(2-phenyl-2-oxoethyl)-4,5-cyclopenteno-thiazolium bromide;
 3-[2-(2,4-dichlorophenyl)-2-oxoethyl]-4,5-cyclopenteno-thiazolium chloride;
 3-[2-(2,4,6-trimethylphenyl)-2-oxoethyl]-4,5-cyclopenteno-thiazolium bromide;
 3-[2-(2,4,6-trimethylphenyl)-2-oxoethyl]-4,5-cyclopenteno-thiazolium bromide;
 3-(2-cyanomethyl)-4,5-cyclohexeno-thiazolium bromide;
 10 3-(2-cyanomethyl)-4,5-cyclopenteno-thiazolium bromide;
 3-(2-cyanomethyl)-4,5-dimethyl-thiazolium bromide;
 3-(2-methyl-2-oxoethyl)-4,5-cyclopenteno-thiazolium chloride;
 3-(2-cyanomethyl)-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;
 3-(2-phenyl-2-oxoethyl)-4-methyl-5-(hydroxyethylsuccinyl)thiazolium chloride;
 15 3-[2-(thien-2-yl)-2-oxoethyl]-2,4,5-trimethylthiazolium bromide;
 3-amino-4-methyl-5-(2-hydroxyethyl)-thiazolium bromide;
 3-(2-phenyl-2-oxoethyl)-2,4,5-trimethylthiazolium chloride;
 3-amino-2,4,5-trimethylthiazolium mesitylenesulfonate;
 3-[2-(4-{2-methoxyphenyl}piperazin-1-yl)-2-oxoethyl]-4,5-dimethylthiazolium
 20 chloride;
 3-[2-hydroxy-2-oxoethyl]-4,5-dimethylthiazolium chloride;
 3-(2-phenyl-2-oxoethyl)-2-aminothiazolium chloride;
 3-[2-(thiomorpholin-4-yl)-2-oxoethyl]-5-hydroxyethyl-4-methylthiazolium
 chloride;
 25 3-[2-(4-trifluoromethylphenyl)-2-oxoethyl]-2,4,5-trimethylthiazolium bromide;
 3-[2-phenyl-2-oxoethyl]-2-isobutylthiazolium chloride;
 3-[2-(thiomorpholin-4-yl)-2-oxoethyl]-2,4,5 trimethylthiazolium chloride;
 3-(2-amino-2-oxoethyl)-2-methylbenzothiazolium chloride;
 3-[2-(4-acetanilino)-2-oxoethyl]-2,4,5-trimethylthiazolium chloride;
 30 3-[2-(4-carboethoxyanilino)-2-oxoethyl]-2,4,5-trimethylthiazolium bromide;
 3-[2-(2,6-diisopropylanilino)-2-oxoethyl]-2,4,5-trimethylthiazolium bromide;
 3-[(4-bromoanilino)-2-oxoethyl]-2,4,5-trimethylthiazolium chloride;
 3-[2-(2-naphthyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-([3-phenylisoxazol-5-yl])-2-oxoethyl]thiazolium bromide;
 3-methyl-4,5-dimethythiazolium chloride;
 3-ethyl-4,5-dimethylthiazolium bromide;
 3-[2-(4'-acetoxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;
 5 3-[2-phenyl-2-oxoethyl]-4-methyl-5-(ethoxycarbonyl)thiazolium chloride;
 3-[2-(4-diethylaminophenyl)-2-oxoethyl]thiazolium chloride;
 1-methyl-3-(2-cyanomethyl)imidazolium bromide ;
 3-(2-cyanomethyl)-4,5-dimethylthiazolium bromide;
 3-(2-cyanomethyl)-4,5-cyclopentenothiazolium bromide;
 10 3-(2-cyanomethyl)-4,5-cyclohexenothiazolium bromide;
 1-methyl-3-(2-cyanomethyl)imidazolium bromide;
 1-vinyl-3-(2-cyanomethyl)imidazolium chloride;
 1-allyl-3-(2-cyanomethyl)imidazolium chloride;
 1-(4-acetylphenyl)-3-(2-cyanomethyl)imidazolium chloride;
 15 1-phenyl-3-(2-cyanomethyl)imidazolium chloride;
 1-(4-methoxyphenyl)-3-(2-cyanomethyl)imidazolium chloride;
 1-(4-methoxycarbonylphenyl)-3-(2-cyanomethyl)-imidazolium chloride;
 3-(2-cyanomethyl)-1-methylbenzimidazolium chloride;
 1,5-dicyclohexyl-3-(2-cyanomethyl)imidazolium bromide;
 20 3-benzyl-oxazol-3-i um bromide.

as well as other biologically or pharmaceutically acceptable salts thereof.

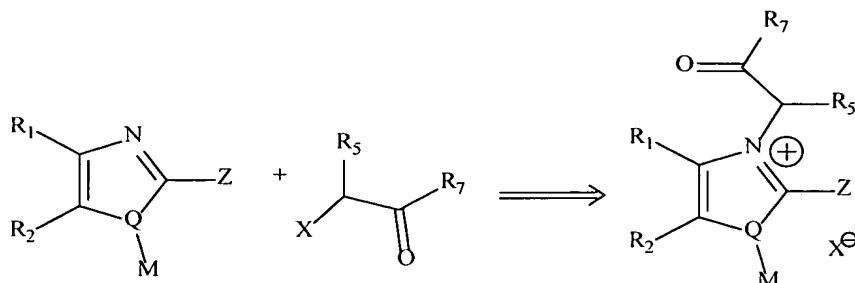
Compounds of the general formula I wherein the R¹, R², X, Y, and Z are defined as above can be prepared by the methods of US 5,656,261; 5,853,703; and 6,007,865; or
 25 as described below. Moreover, certain of the compounds are conveniently prepared by chemical syntheses that are well-known in the art. In addition, certain of the compounds are well-known and readily available from chemical supply houses or can be prepared by synthetic methods specifically published therefor. The chemical reagents shown in the schemes below provide nonlimiting examples of means well known in the art to carry out the reaction steps shown.

Compounds of the invention wherein Y is CH(R⁵)-C(O)-R⁷ can be prepared according to the synthetic route depicted in **Scheme 1** (wherein R¹, R², R⁵, R⁷, M, Q, and Z are as described above, and X is a halide). An acetyl derivative with a suitable a α

2002-04-22 10:45:10

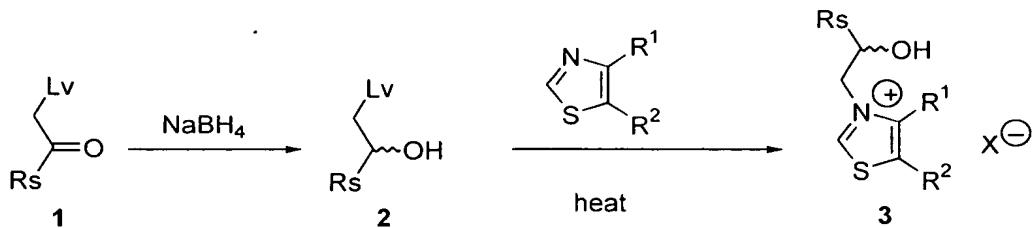
leaving group, for example, an α -halo acetyl derivative, can be used to alkylate a suitably substituted thiazole, oxazole, or imidazole. The alkylation reaction may be conducted at elevated temperatures in a suitable solvent, for example, acetonitrile or ethanol, or without solvent.

5

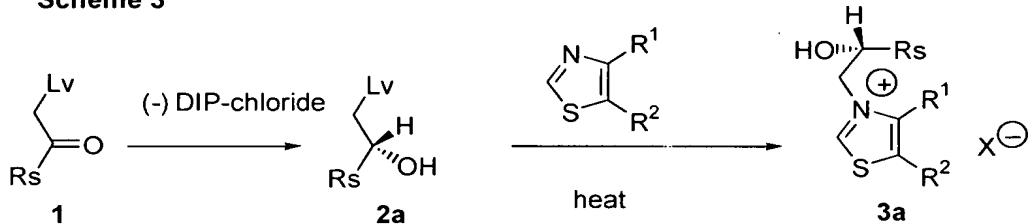


Compounds of the invention wherein R^7 is a group of the formula $-CH(OH)R_s$ may be prepared as shown in **Schemes 2** and **3** (see below). In the nonlimiting exemplary synthetic schemes below, some product compounds are shown as specific 10 optical isomers and others are shown as racemic compounds. One skilled in the art will appreciate that appropriate reaction conditions and reagents, that are well known in the art, can be used to customize the degree of reaction stereoselectivity. Thus, isolated stereoisomers are within the scope of compounds of the invention. For example, compound **2** can be obtained as a racemic mixture from compound **1** or as an **S** 15 (**compound 2a**) or **R** stereoisomer depending on the reducing agent employed. Substitution of comparable reagents to achieve different stereoselectivity, even when not shown explicitly by the scheme, is well known in the art at the time of filing. Moreover, synthetic processes and stereoselective purifications, such as chromatography on stereoselective media can be used to achieve 90%, 95%, 98%, 99% or better isomeric 20 purity, such that compositions substantially free of the non-desired isomer can be prepared.

A synthetic scheme for making compounds of the formula I wherein Y is $CH_2CH(OH)R_s$ is shown in **Scheme 2**. A hydroxyl is incorporated into a nucleophile used to derivatize a thiazole compound, as follows:

Scheme 2

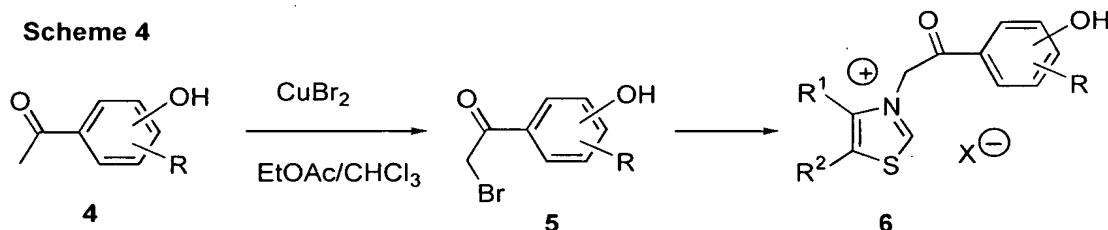
where Lv is a leaving group such as chloro. In a related synthesis, Compound 1 is reduced with a stereoselective reducing agent such as (-) DIP-chloride [(-)-B-chlorodiisopinocampheylborane] or (+) DIP-chloride [(+)-B-chlorodiisopinocampheylborane]. For example:

Scheme 3

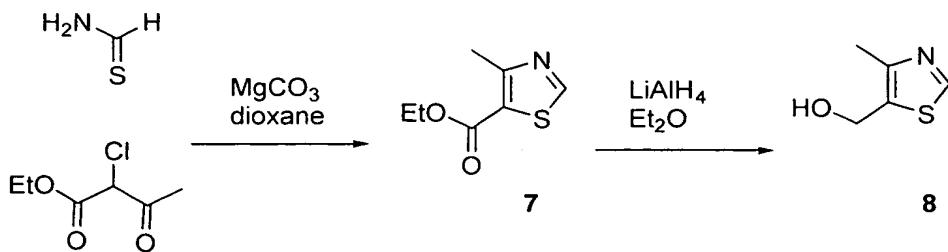
Substitution of (+) DIP-chloride results predominately in the mirror image to compound 3a.

Scheme 4 exemplifies methods of preparing compounds of the formula I wherein Y is a group of the formula $-\text{CH}_2\text{R}^6$ wherein R^6 is a substituted or unsubstituted benzoyl moiety. In this particular preparation, acetophenones substituted in the phenyl moiety with hydroxy groups are derivatized to add a leaving group to the alpha methyl group, and the resulting intermediate is then used to alkylate thiazoles, as exemplified below:

15

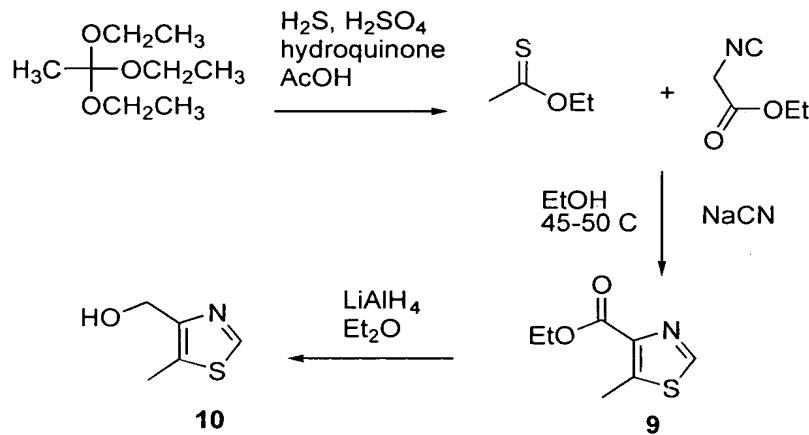
Scheme 4

In another synthesis, the preparation of compounds of the formula I wherein R^2 is $-\text{CH}_2\text{OH}$ are exemplified. Formamide is first converted to thioformamide by reaction with phosphorus pentasulfide. Thioformamide is reacted with ethyl 2-chloroacetoacetate in dry dioxane as follows:

Scheme 5

Compound **8** can then be reacted with a suitable alkylating agent to make a compound of the invention.

Where R^1 is $-\text{CH}_2\text{OH}$ and R^2 is $-\text{CH}_3$ in Formula I, the route shown in **Scheme 6** 5 can be used. The preparation of a thiazole analog containing a 4-hydroxymethyl group, for example, is shown below:

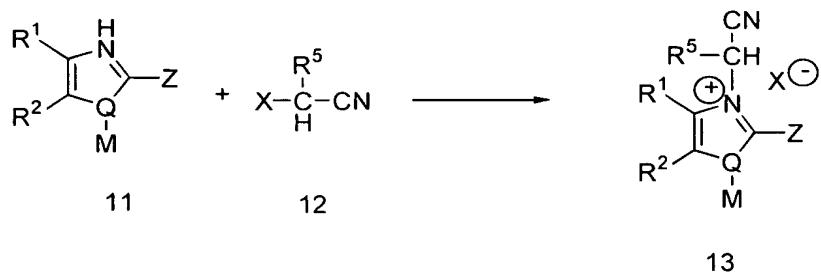
Scheme 6

Compound **10** can then be alkylated with a suitable alkylating agent to make a compound 10 of the invention.

Note that reaction conditions indicated in the various reaction schemes are exemplary: such conditions as solvent and temperature are subject to modification within ordinary skill.

A useful synthetic route for the preparation of compounds of formula I wherein Y 15 is $-\text{CH}(\text{R}^5)\text{CN}$ is shown in **Scheme 7**.

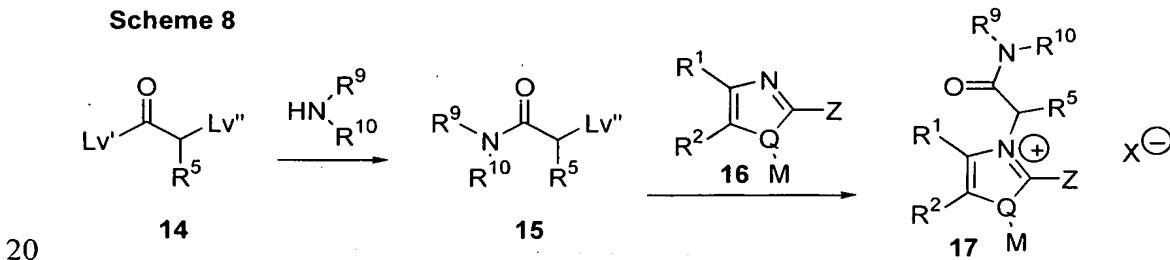
Scheme 7



wherein M, Q, R¹, R², R⁵, Y and Z are as described in the text above, and X is a halide, mesitylenesulfonate or other biologically acceptable anion. In **Scheme 7**, the appropriately substituted imidazole, oxazole, or thiazole of formula **11** is contacted with 5 a (e.g.) halo substituted acetonitrile of formula **12** to produce compounds of the formula **13**. The reaction can be performed without any added solvent, or an anhydrous solvent can be utilized as the solvent medium. When a solvent is used, acetonitrile is a typical solvent for this reaction. Reaction times vary according to particular reactants and conditions, but are usually in the range of a few minutes to 48 hours at a temperature of 10 25-130°C.

Compounds of the formula **17** (below), wherein Y contains a carboxamido moiety, can be synthesized according to method depicted in **Scheme 8**. An appropriately substituted amine can be condensed with an activated acetyl analog (for example, an acid chloride or acid anhydride), containing an additional leaving group alpha to the carbonyl 15 group, to provide the carboxamide **15**. Compound **15** can then be used to alkylate the heterocycle **16** to yield a compound of the invention **17**. For oxazole-based compounds, reaction temperatures may be reduced over those used for thiazole-based compounds, especially where the oxazole reactant is highly volatile.

Scheme 8



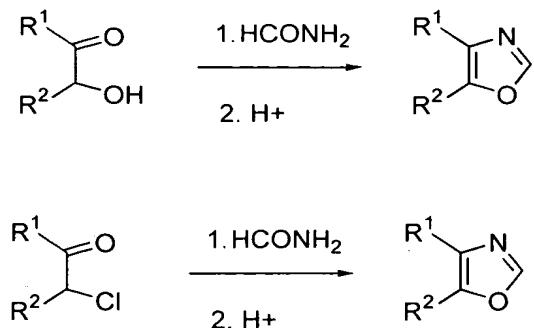
Other alkylation conditions can also be used. For example, thiazoles and imidazoles can be alkylated at the 1-position or the 2-position by vapor phase alkylation over an appropriate solid catalyst, using the corresponding alcohol as the alkyl source. *See, Ono et al., in Catalysis by Microporous Materials, Studies in Surface Science and Catalysis, Vol. 94, Beyer et al., Eds., 1995, polypeptide 697-704.* Appropriate catalysts include zeolite H-Y, zeolite H-ZSM-5 and H₃PW₁₂O₄₀ supported on silica. Reaction conditions typically include high temperatures, such as 260 and 300 °C.

In addition, N-aryl substituted thiazoliums, oxazoliums and imidazoliums can also be prepared. For example, fluoro phenyl compounds such as 4-fluorobenzoic acid 10 methyl ester can be used to substitute the N¹ nitrogen of imidazole to make methyl-4-(1H-imidazol-1-yl)benzoate. *See, Morgan et al., J. Med. Chem. 33: 1091-1097, 1990.* These aryl substituted imidazoliums can then be reacted with an alkylating agent, for example, an α-haloacetophenone analog, to prepare a compound of the invention. Also, the amine functions of imidazoles or amine-substituted thiazoles can be acylated by 15 dehydration or other methods known in the art.

3-Aminothiazoliums, 3-aminooxazoliums, and 1-alkyl-3-aminoimidazoliums can be prepared by reaction with O-mesitylene sulfonylhydroxylamine in methylene chloride. The product mesitylenesulfonate salts can be converted to their chloride salts through ion exchange with strongly basic anion exchange resins.

Substituted oxazole intermediate that are suitable intermediates for the alkylation reactions, such as those shown in **Schemes 1** and **7**, can be prepared by methods known in the art. For instance, 2-unsubstituted oxazoles can be formed by condensation of formamide with either α-hydroxy or α-haloketones intermediates (H. Bredereck, R. Gompper, H. G. v. Shuh and G. Theilig, in *Newer Methods of Preparative Organic Chemistry*, Vol. III, ed. W. Foerst, Academic press, New York, 1964, p. 241). The 25 intermediates can cyclize under acid conditions to form the oxazole ring (**Scheme 9**). In addition, 2,4-disubstituted oxazoles can be prepared from α-haloketones and amides at higher temperatures using the same method.

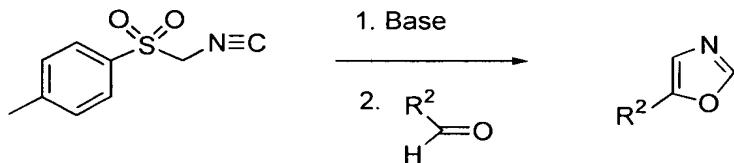
10001442007

Scheme 9

Oxazoles can be prepared by cyclization reactions of isonitriles (van Leusen, A.

M. *Lect. Heterocycl. Chem.* **1980**, *5*, S111; Walborsky, H. M.; Periasamy, M. P. in *The 5. Chemistry of Functional Groups, suppl. C*, Patai, S., Rappoport, Z., Eds, Wiley-Interscience, 1983, p. 835; Hoppe, D. *Angew. Chem. Int. Edn. Engl.*, **1974**, *13*, 789; Schollkopf, U. *Angew. Chem. Int. Ed. Engl.*, **1977**, *16*, 339). For example, as shown below in **Scheme 10**, the tosylmethyl isocyanide can be deprotonated by a base and reacted with a suitable electrophile (e.g. an aldehyde). The intermediate can cyclize and 10 aromatize to provide the desired oxazole intermediate. The intermediate can then be N-alkylated by the above-described methods to furnish a compound of the invention. Other methods for preparing oxazole intermediates include 1,5-dipolar cyclization of acylated nitrile ylides (Taylor E. C.; Turchi, I. J. *Chem. Rev.*, **1979**, *79*, 181; Huisgen, R. *Angew. Chem. Int. Edn. Engl.* **1980**, *19*, 947).

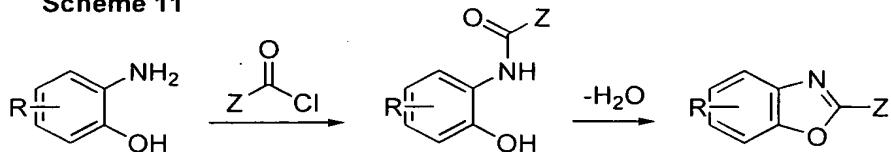
15

Scheme 10

Benzoxazole intermediates substituted at the 2 position can be prepared from 2-

20 aminophenols by acylation with, for example, with an acid chloride and cyclization (**Scheme 11**). The intermediate can then be N-alkylated by the above-described methods to furnish a compound of the invention.

Scheme 11



To treat the indications of the invention, an effective amount of a pharmaceutical compound will be recognized by clinicians but includes an amount effective to treat,

5 reduce, ameliorate, eliminate or prevent one or more symptoms of the disease sought to be treated or the condition sought to be avoided or treated, or to otherwise produce a clinically recognizable change in the pathology of the disease or condition.

Pharmaceutical compositions can be prepared to allow a therapeutically effective quantity of the compound of the present invention, and can include a pharmaceutically

10 acceptable carrier, selected from known materials utilized for this purpose. *See, e.g.,* Remington, The Science and Practice of Pharmacy, 1995; Handbook of Pharmaceutical Excipients, 3rd Edition, 1999. Such compositions can be prepared in a variety of forms, depending on the method of administration, such as sublingual, rectal, nasal, vaginal, topical (including the use of a patch or other transdermal delivery device), by pulmonary 15 route by use of an aerosol, or parenteral, including, for example, intramuscular, subcutaneous, intraperitoneal, intraarterial, intravenous or intrathecal..

In addition to the subject compound, the compositions of this invention can contain a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier", as used herein, means one or more compatible solid or liquid filler diluents or 20 encapsulating substances that are suitable for administration to an animal, including a mammal or human. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the subject compound, and with each other, such that there is no interaction that would substantially reduce the pharmaceutical efficacy of the composition under ordinary use. Preferably when liquid 25 dose forms are used, the compounds of the invention are soluble in the components of the composition. Pharmaceutically-acceptable carriers should, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the animal being treated.

Some examples of substances which can serve as pharmaceutically-acceptable 30 carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches,

100-244-122-01

such as corn starch and-potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil,

5 corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the TweenTM brand emulsifiers; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents, stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions. The choice of a pharmaceutically-acceptable carrier to be used in conjunction with the subject compound is basically determined by the way the compound is to be administered. If the subject compound is to be injected, the preferred pharmaceutically-acceptable carrier is sterile, physiological saline, with a blood-compatible suspending agent, the pH of which has been adjusted to about 7.4.

10 15 If the preferred mode of administering the subject compound is perorally, the preferred unit dosage form is therefore tablets, capsules, lozenges, chewable tablets, and the like. Such unit dosage forms comprise a safe and effective amount of the subject compound, which is preferably from about 0.7 or 3.5 mg to about 280 mg/ 70 kg, more preferably from about 0.5 or 10 mg to about 210 mg/ 70 kg. The pharmaceutically-acceptable carrier suitable for the preparation of unit dosage forms for peroral administration are well-known in the art. Tablets typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmelose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder-mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules typically comprise one or more solid diluents disclosed above. The

20 25 30 selection of carrier components depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of this invention, and can be readily made by a person skilled in the art.

Peroral compositions also include liquid solutions, emulsions, suspensions, and the like. The pharmaceutically-acceptable carriers suitable for preparation of such compositions are well known in the art. Such liquid oral compositions preferably comprise from about 0.012% to about 0.933% of the subject compound, more preferably 5 from about 0.033% to about 0.7%. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, cellulose (e.g. Avicel™, RC-591), tragacanth and sodium alginate; typical wetting agents include lecithin and 10 polyethylene oxide sorbitan (e.g. polysorbate 80). Typical preservatives include methyl paraben and sodium benzoate. Peroral liquid compositions may also contain one or more components such as sweeteners, flavoring agents and colorants disclosed above.

Other compositions useful for attaining systemic delivery of the subject compounds include sublingual and buccal dosage forms. Such compositions typically 15 comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

Compositions can also be used to deliver the compound to the site where activity 20 is desired; such as eye drops, gels and creams for ocular disorders.

Compositions of this invention include solutions or emulsions, preferably aqueous solutions or emulsions comprising a safe and effective amount of a subject compound intended for topical intranasal administration. Such compositions preferably comprise from about 0.01% to about 10.0% w/v of a subject compound, more preferably 25 from about 0.1% to about 2.0%. Similar compositions are preferred for systemic delivery of subject compounds by the intranasal route. Compositions intended to deliver the compound systemically by intranasal dosing preferably comprise similar amounts of a subject compound as are determined to be safe and effective by peroral or parenteral administration. Such compositions used for intranasal dosing also typically include safe 30 and effective amounts of preservatives, such as benzalkonium chloride and thimerosal and the like; chelating agents, such as edetate sodium and others; buffers such as phosphate, citrate and acetate; tonicity agents such as sodium chloride, potassium chloride, glycerin, mannitol and others; antioxidants such as ascorbic acid, acetylcystine,

sodium metabisulfite and others; aromatic agents; viscosity adjustors, such as polymers, including cellulose and derivatives thereof; and polyvinyl alcohol and acids and bases to adjust the pH of these aqueous compositions as needed. The compositions may also comprise local anesthetics or other actives. These compositions can be used as sprays, mists, drops, and the like.

Other preferred compositions of this invention include aqueous solutions, suspensions, and dry powders comprising a safe and effective amount of a subject compound intended for atomization and inhalation administration. Such compositions are typically contained in a container with attached atomizing means. Such compositions also typically include propellants such as chlorofluorocarbons 12/11 and 12/114, and more environmentally friendly fluorocarbons, or other nontoxic volatiles; solvents such as water, glycerol and ethanol, including cosolvents as needed to solvate or suspend the active agent; stabilizers such as ascorbic acid, sodium metabisulfite; preservatives such as cetylpyridinium chloride and benzalkonium chloride; tonicity adjustors such as sodium chloride; buffers; and flavoring agents such as sodium saccharin. Such compositions are useful for treating respiratory disorders, such as asthma and the like.

Other preferred compositions of this invention include aqueous solutions comprising a safe and effective amount of a subject compound intended for topical ocular administration. Such compositions preferably comprise from about 0.01% to about 0.8% w/v of a subject compound, more preferably from about 0.05% to about 0.3%. Such compositions also typically include one or more of preservatives, such as benzalkonium chloride or thimerosal; vehicles, such as poloxamers, modified celluloses, povidone and purified water; tonicity adjustors, such as sodium chloride, mannitol and glycerin; buffers such as acetate, citrate, phosphate and borate; antioxidants such as sodium metabisulfite, butylated hydroxy toluene and acetyl cysteine; acids and bases can be used to adjust the pH of these formulations as needed.

Other preferred compositions of this invention useful for peroral administration include solids, such as tablets and capsules, and liquids, such as solutions, suspensions and emulsions (preferably in soft gelatin capsules), comprising a safe and effective amount of a subject compound. Such compositions can be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject compound is released in the gastrointestinal tract at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate

phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, EudragitTM coatings, waxes and shellac.

The compounds of the invention are administered by ocular, oral, parenteral, including, for example, using formulations suitable as eye drops. For ocular

5 administration, ointments or droppable liquids may be delivered by ocular delivery systems known to the art such as applicators or eye droppers. Such compositions can include mucomimetics such as hyaluronic acid, chondroitin sulfate, hydroxypropyl methylcellulose or polyvinyl alcohol, preservatives such as sorbic acid, EDTA or benzylchromium chloride, and the usual quantities of diluents and/or carriers. See,
10 Remington's Pharmaceutical Sciences, 16th Ed., Mack Publishing, Easton, PA, 1980, as well as later editions, for information on pharmaceutical compounding.

Numerous additional administration vehicles will be apparent to those of ordinary skill in the art, including without limitation slow release formulations, liposomal formulations and polymeric matrices.

15 In another preferred embodiment, the pharmaceutically effective amount is approximately 0.1 or 0.5 to 4 mg/kg body weight daily. Still more preferably, the pharmaceutically effective amount is approximately 1 mg/kg body weight daily. In a preferred embodiment, the amount is administered in once daily doses, each dose being approximately 1 mg/kg body weight.

20 The activity of the compounds of the invention in breaking, reversing or inhibiting the formation of AGE's or AGE-mediated crosslinks can be assayed by any of the methods described in US Patent 5,853,703.

The following examples further illustrate the present invention, but of course, should not be construed as in any way limiting its scope.

25

Example

Rats received a daily intraperitoneal dose of 10 mg/kg 3-[2-phenyl-2-oxoethyl]-4,5-dimethyl-thiazolium salt (compound A) (n=14) or placebo (n=15) for 30 days. The animals then underwent a thoracotomy and the left anterior descending coronary artery ligated. The chest was then closed and the animals allowed to recover for 14 days while continuing to be treated with compound A or placebo. The animals were then sacrificed and the hearts removed for histological examination. The weight of the infarcted tissue was 0.16 ± 0.04 g for the placebo treated animals compared to 0.11 ± 0.05 g for the compound A treated animals.

A treated animals ($p=0.04$). The thickness of the ventricular wall in the infarcted zone was also reduced in the compound A treated animals compared to placebo ($2.72\pm.13$ mm vs. $2.56\pm.22$ mm, $p=0.09$).

5 **EXAMPLE 1. 3-(2-Phenyl-2-hydroxyethyl)-4,5-dimethylthiazolium chloride: 2-Chloro-1-phenylethanol:**

2-Chloroacetophenone (5.0 g, 32 mmol) was dissolved in methanol (25 mL) and cooled to 0°C . Sodium borohydride (1.2 g, 32 mmol) was added and stirred at 0°C for 30 minutes. The reaction mixture was neutralized by adding conc. HCl to pH 7.0 and 10 evaporated to dryness. The residue was dissolved in ethanol (30 mL) and filtered, washed with ethanol. The ethanol was evaporated to dryness. The residue was dissolved in methylene chloride (20 mL) and dried over sodium sulfate. The methylene chloride solution was filtered and evaporated to give the desired product as an oil; yield 4.84 g (5.6%).

15 **3-(2-Phenyl-2-hydroxyethyl)-4,5-dimethylthiazolium chloride:**

The neat mixture of 2-chloro-1-phenylethanol (2.34 g, 14.9 mmol) and 4,5-dimethylthiazole (1.69 g, 14.9 mmol) were heated with stirring at 135°C for 28 hrs. It was cooled to room temperature and water (30 mL) was added to the reaction mixture with stirring, and then was extracted with ether (30 mL). The water layer was treated 20 with activated carbon and evaporated to dryness. It was crystallized from a mixture of acetonitrile and ether to give a racemic product as prisms; 0.39 g (9.7%); mp. 201-203°C.

EXAMPLE 2. S 3-(2-Phenyl-2-hydroxyethyl)-4,5-dimethylthiazolium chloride:

S (-) 2-chloro-1-phenylethanol.

25 2-Chloroacetophenone (3 g., 19.4 mmol) was treated with (-) DIP-chloride (6.7 g., 20.9 mmol) in anhydrous THF (20 mL) at dry-ice bath temperature and left overnight. The temperature was raised to room temperature and THF was removed in vacuo. The residue was dissolved in ether (100 mL). The diethanolamine (4.58 g., 42.6 mmol) was added and the mixture stirred at room temperature for 5 hrs. The separated solid was 30 filtered and the filtered cake was washed with hexane (40 mL) and ether (30 mL). The

combined filtrates were evaporated to dryness to give 6.36 g of crude product. This was purified by silica gel column chromatography using 1 % ether and petroleum ether 1.71 g (56 %) of the desired product was obtained as an oil.

S 3-(2-Phenyl-2-hydroxyethyl)-4,5-dimethylthiazolium chloride.

5 The neat mixture of S (-) 2-chloro-1-phenylethanol (2.78 g., 17.8 mmol) and 4,5-dimethylthiazole (2 g., 17.7 mmol) were heated with stirring at 135°C for 25 hrs. It was cooled to room temperature and water (30 mL) was added to the reaction mixture with stirring. The solution was extracted with ether (30 mL). The ether extract was again extracted with water (30 mL). The combined water layer was evaporated to dryness and
 10 the residue was crystallized with a mixture of acetonitrile and methyl tert-butyl ether.

Yield: 0.63 g. (7.7 %); mp. 189-190°C; $[\alpha]_D^{25} -51.765$ (Water, $c = 1.7732$).

EXAMPLE 3. R(+)-3-(2-Phenyl-2-hydroxyethyl)-4,5-dimethylthiazolium chloride:

R(+) 2-chloro-1-phenylethanol.

2-Chloroacetophenone (6.25 g., 40.4 mmol) was treated with (+) DIP-chloride (18 g., 56.1 mmol) in anhydrous THF (40 mL) at dry-ice bath temperature and left overnight. The temperature was raised to room temperature and THF was removed in *vacuo*. The residue was dissolved in ether (210 mL). The diethanolamine (9 g., 8.56 mmol) was added and the mixture stirred at room temperature for 5 hrs. The separated solid was filtered and the filtered cake was washed with ether (150 mL). The combined filtrates were evaporated to dryness to give 15.53 g. of crude product. This was purified by silica gel column chromatography using 1 % ether and petroleum ether 4.32 g (68 %) of the desired product as an oil.

R (+) 3-(2-Phenyl-2-hydroxyethyl)-4,5-dimethylthiazolium chloride.

The neat mixture of R (+) 2-chloro-1-phenylethanol (4.32 g., 27.6 mmol) and 4,5-dimethylthiazole (3.12 g, 27.6 mmol) were heated with stirring at 135°C for 25 hrs. It was cooled to room temperature and water (30 mL) was added to the reaction mixture with stirring. The solution was extracted with ether (30 mL). The ether extract was again extracted with water (30 mL). The combined water layer was evaporated to

dryness and the residue was crystallized with a mixture of acetonitrile and methyl tert-butyl ether. Yield: 0.44 g. (5.4 %); mp. 187-189°C; $[\alpha]_D^{25} +52.009$ (Water, c = 1.7824).

EXAMPLE 4. 3-[2-(2', 3' or 4'-monohydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide.

5 **2-Bromo-4'-hydroxyacetophenone.**

Copper (II) bromide (6 g, 26.9 mmol) was suspended in ethyl acetate (50 mL) and 4'-hydroxyacetophenone (2 g, 14.7 mmol) dissolved in chloroform (20 mL) was added to the suspension. The reaction mixture was refluxed for 8 hrs. and filtered hot through celite pad. The filtrate was evaporated to dryness to give the desired crude brown 10 colored compound (mp=115-118°C; yield: 3.03 g, 96%). The NMR spectrum and TLC [silica gel, Hexanes:EtOAc (1:1, v/v)] was in agreement with the desired product. It was used as such in the next step of the reaction without further purification.

This method was used to prepare:

(i) 2-Bromo-2'-hydroxyacetophenone from 2'-hydroxyacetophenone and copper (II) 15 bromide. Yield: 3.30 g. (95%; oil).

(ii) 2-Bromo-3'-hydroxyacetophenone from 3'-hydroxyacetophenone and copper (II) bromide. Yield: 3.20 g. (92%; oil).

3-[2-(4-Hydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide.

The neat mixture of 2-bromo-4'-hydroxyacetophenone (3 g, 15 mmol) and 4,5-dimethylthiazole (1.71 g, 15 mmol) was heated at 110°C for 3 hrs. It was dissolved in 20 acetonitrile (15 mL) and cooled to room temperature. Tert-butyl methyl ether (5 mL) was added and the reaction mixture kept at room temperature overnight. The product crystallized was filtered, washed well with a mixture of acetonitrile and tert-butyl methyl ether (1:1, v/v) and dried. It was recrystallized from a mixture of acetonitrile, ethyl 25 alcohol and tert-butyl methyl ether. Yield: 3.18 g (64%); mp. 245-247°C (dec.).

This method was used to prepare:

(i) 3-[2-(2-Hydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide from 2-bromo-2'-hydroxyacetophenone and 4,5-dimethylthiazole. Yield: 2.05 g. (38%), mp = 208-209°C.

(ii) 3-[2-(3-Hydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide from 2-bromo-3'-hydroxyacetophenone and 4,5-dimethylthiazole. Yield: 1.52 g. (47%), mp = 235-237°C.

5 **EXAMPLE 5.** 3-(2-Phenyl-2-oxoethyl)-4-methyl-5-(hydroxymethyl)thiazolium chloride.

Thioformamide.

To formamide (20 g, 443 mmol) dissolved in anhydrous THF (100 mL) was added phosphorous pentasulfide (P_2S_5) (20 g, 45 mmol) while maintaining the temperature at 10 30-35°C. The mixture was stirred overnight at room temperature, filtered and stripped of THF. The crude product was suspended in ethyl acetate (40 mL) and cooled at -78°C overnight, filtered and dried in vacuo at room temperature to give thioformamide (10.6 g, 39%). See Rynbrandt, R.H., Nishizawa, E.E., Balogoyen, D.P., Mezdoza, A.K., Annis, K.A.; *J. Med. Chem.* **1981**, 24, 1507-1510.

15

4-Methyl-5-(ethoxycarbonyl)thiazole.

Thioformamide (7.5 g, 122.72 mmol), ethyl 2-chloroacetoacetate (16.4 g, 99.52 mmol) and magnesium carbonate (20 g, 237.22 mmol) were taken dioxane (100 mL) and heated at 110°C for 4 hrs. The reaction mixture was cooled to room temperature and 20 filtered to remove magnesium carbonate. The solvent was evaporated to dryness and the residue was taken in ether (200 mL) and washed successively with 0.5 M NaOH solution (200mL x 2) and saturated brine solution (100 mL) and dried over Na_2SO_4 . It was filtered and evaporated to give 4-methyl-5-(ethoxycarbonyl)thiazole as an oil which was purified by silica gel column chromatography using hexanes:EtOAc (8:2, v/v) as a 25 eluent; yield: 3.28 g (17%).

4-Methyl-5-(hydroxymethyl)thiazole.

A 250-mL, three necked round-bottomed flask fitted with a 100-mL dropping funnel, a nitrogen-inlet tube, and a reflux condenser was added lithium aluminum hydride (1 g, 30 26.35 mmol) and anhydrous ether (50mL). To the dropping funnel was added 4-methyl-5-(ethoxycarbonyl)-thiazole (3 g, 17.3 mmol) and anhydrous ether (25 mL). While the

suspension of lithium aluminum hydride was gently stirred under a nitrogen atmosphere, the solution of 4-methyl-5-(ethoxycarbonyl)thiazole was added dropwise at a rate maintaining a gentle reflux. When the addition was complete, the mixture was heated at reflux for 4 hrs. After the mixture had returned to room temperature, anhydrous ether 5 (100 mL) was added. The gray reaction mixture was hydrolyzed by addition, in small parts, of a sufficient amount of wet sodium sulfate. The reaction mixture was filtered through a sintered-glass funnel. The organic layer separated and dried over Na_2SO_4 . It was filtered and evaporated to give desired compound as an oil; yield: 590 mg (26%).

10 **3-(2-Phenyl-2-oxoethyl)-4-methyl-5-(hydroxymethyl)thiazolium chloride.**

The neat reaction of 4-methyl-5-(hydroxymethyl)thiazole (590 mg, 4.57 mmol) and 2-chloroacetophenone (710 mg, 4.59 mmol) was heated at 110°C. The mixture solidified within 15 minutes. Acetonitrile (10 mL) was added and the mixture refluxed for another 3 hrs. It was cooled to room temperature and tert-butyl methyl ether (5 mL) was added 15 and the reaction mixture was left overnight at room temperature. The product crystallized was filtered and washed well with a mixture of hexanes: EtOAc (1:1, v/v) and dried. It was recrystallized from a mixture of acetonitrile/ethanol/ tert-butyl methyl ether; yield 130 mg (10%); mp.240-242°C (dec.).

EXAMPLE 6. 3-[2-(Disubstituted-dihydroxyphenyl)-2-oxoethyl]-4-

20 **dimethylthiazolium bromide.**

2-Bromo-2',4'-dihydroxyacetophenone.

Copper (II) bromide (6 g, 26.9 mmol) was suspended in ethyl acetate (50 mL) and 2',4'-dihydroxyacetophenone (2 g, 13.1 mmol) dissolved in chloroform (20 mL) was added to the suspension. The reaction mixture was refluxed for 8 hrs. and filtered hot through 25 celite pad. The filtrate was evaporated to dryness to give crude oil (3.0 g, 96%). The NMR spectrum and TLC [silica gel, Hexanes:EtOAc (1:1, v/v)] was in agreement with the desired product. It was used as such in the next step of the reaction without further purification.

This method was used to prepare:

30 (i) 2-Bromo-3',5'-dihydroxyacetophenone from 3',5'-dihydroxyacetophenone and copper (II) bromide.

(ii) 2-Bromo-2',5'-dihydroxyacetophenone from 2',5'-dihydroxyacetophenone and copper (II) bromide. Yield: 2.99g; 99%

3-[2-(2,4-Dihydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide.

5 The neat mixture of 2-bromo-2',4'-dihydroxyacetophenone (3 g, 13 mmol) and 4,5-dimethylthiazole (1.71 g, 13.3 mmol) was heated at 110°C for 3 hrs. It was dissolved in acetonitrile (15 mL) and cooled to room temperature. Tert-butyl methyl ether (5 mL) was added and the reaction mixture kept at room temperature overnight. The product crystallized was filtered, washed well with a mixture of acetonitrile and tert-butyl methyl ether (1:1, v/v) and dried. It was recrystallized from a mixture of methanol and a few drops of water. Yield: 2.5 g (50%); mp. 257-260°C (dec.).

10

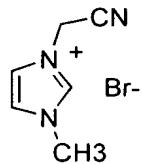
This method was used to prepare:

(i) 3-[2-(3,5-Dihydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide in 55% yield from 2-bromo-3',5'-dihydroxyacetophenone and 4,5-dimethylthiazole; mp. 257-258°C. Yield: 2.05 g (21%).

15 (ii) 3-[2-(2,5-Dihydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide in 57% yield from 2-bromo-2,5-dihydroxyacetophenone and 4,5-dimethylthiazole; mp. 231-232°C. Yield: 4.03 g (52%).

20 (iii) 3-[2-(3,4-Dihydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride in 60% yield from commercially available 2-chloro-3',4'-dihydroxyacetophenone and 4,5-dimethylthiazole; mp. 260-263°C (dec.); yield: 3.9 g (48%).

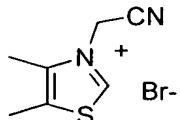
EXAMPLE 7. Preparation of 1-methyl-3-(cyanomethyl)imidazolium bromide



A mixture of 1-methylimidazole (1 g, 12.2 mmol) and bromoacetonitrile (1.46 g, 12.2 mmol) were combined and stirred. An exothermic reaction was produced and the product precipitated from the reaction mixture. After cooling the reaction mixture is allowed to cool to room temperature acetonitrile (CH₃CN) (2 mL) is added. The crude

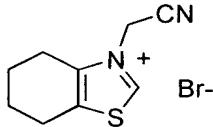
product is recovered by filtration and washed with additional CH_3CN . The crude product is dissolved in H_2O , treated with decolorizing carbon and evaporated in vacuo to dryness. The product is further purified by recrystallization from a mixture of ethanol EtOH , CH_3CN and diethyl ether to yield 1-methyl-3-(2-cyanomethylene)-imidazolium bromide as a white crystalline solid: mp 165-167 °C.

Example 8. Preparation of 3-(cyanomethyl)-4,5-dimethylthiazolium bromide



A mixture of 4,5-dimethylthiazole and bromoacetonitrile were heated with stirring at 95 °C for 1 hour. The product precipitated from the mixture within 30 minutes. After cooling to room temperature, the product a solution of 30% v/v of diethyl ether: CH₃CN (10 mL) was added with stirring. The crude product was recovered by filtration, and recrystallized from a mixture of EtOH and CH₃CN to yield 2.136 g of 3-(cyanomethyl)-4,5-dimethylthiazolium bromide as needles: mp 184-186 °C (dec.).

Example 9. Preparation of 3-(cyanomethyl)-4,5-cyclohexenothiazolium bromide



A mixture of thioformamide (0.8 g), 2-chlorocyclohexan-1-one (1.73 g), $MgCO_3$ (1.5 g) was refluxed in dioxane (12 mL) for 30 h. The reaction mixture was evaporated in vacuo, and the concentrated poured into diethyl ether (30 mL). The resulting ethereal solution was washed with 1% NaOH solution (3 x 15 mL). The combined NaOH solution was back extracted with diethyl ether. The ether layers were combined, washed with saturated NaCl soution until neutral, and then dried over Na_2SO_4 . The ethereal solution was evaporated in vacuo to afford 1.02 g of 4,5-cyclohexenothiazole.

25 A mixture of 4,5-cyclohexenothiazole (1 g, 7.2 mmol) and bromoacetonitrile (0.863 g, 7.2 mmol) were heated at 120 °C for 1 h. After cooling the reaction mixture was treated with a solution of 30% diethyl ether in CH₃CN (10 mL). The product was recovered by filtration and washed with additional 30% diethyl ether in CH₃CN. The product was recrystallized from a mixture of EtOH and CH₃CN to yield 0.752 g of 3-

(cyanomethyl)-4,5-cyclohexenothiazolium bromide as a crystalline solid: mp 215-217 °C (dec.).

The preparation of 3-(2-cyanomethyl)-4,5-cyclopentenothiazolium bromide from 2-chlorocyclopentan-1-one is conducted as in the above procedure.

5

Example 10. Preparation of 3-[2-(1-pyrrolidinyl)-2-oxoethyl]-1,2-dimethylimidazolium chloride

N-(chloroacetyl)pyrrolidine

Pyrrolidine (63.9 g, 0.9 mole) was taken up in CH_2Cl_2 (640 mL) and cooled to 0 10 °C in a salt-ice water bath. To the stirred mixture was added chloroacetyl chloride (101.8 g in 450 mL of CH_2Cl_2 , 0.9 mole) dropwise maintaining the internal temperature below 15 °C. After adding the chloroacetyl chloride, the mixture was stirred for one hour at 5 °C. Sodium hydroxide solution (7 M, 190 mL) was added with vigorous stirring such that the inside temperature did not exceed 20 °C. The mixture was stirred 15 for 15 minutes and the aqueous layer was separated. The organic layer was washed with saturated sodium bicarbonate solution (2 x 200 mL), water (1 x 200 mL) and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the residue was recrystallized from hexane to give 64.5 g (48.6% yield) of white plate crystals; mp 43 °C.

20

3-[2-(1-pyrrolidinyl)-2-oxoethyl]-1,2-dimethylimidazolium chloride

A mixture of N-(chloroacetyl)pyrrolidine (2.0 g, 13.55 mmol) and 1,2-dimethylimidazole (1.3 g, 13.5 mmol) were heated neat at 110 °C for 3 hours. To the reaction mixture was added acetonitrile (5 mL), and heating was continued for 20 minutes. Tert-butyl 25 methylether (10 mL) was added, and the resulting mixture was allowed to stand at room temperature overnight. The product was recovered by filtration, and washed with a mixture of tert-butyl methyl ether and acetonitrile (7:3 v/v, 50 mL). The crude product was recrystallized from a mixture of acetonitrile and tert-butyl methyl ether to obtain 1.23 g (41%) of a white solid; mp 191-193°C.

30

Example 11. Preparation of 1-butyl-3-aminoimidazolium mesitylene sulfonate

100331-510A

An ice-cold solution of 1-butylimidazole (7.0 g, 16.30 mmol) in anhydrous CH₂Cl₂ (35 mL) was treated dropwise with a solution of O-mesitylene sulfonylhydroxylamine (17.8 g, 16.50 mmol) in CH₂Cl₂ (70 mL). After stirring for 6 hours in the ice-bath, ether (210 mL) was added with stirring over the course of 1 hour.

5 The resulting mixture was allowed to stand at -16 °C overnight. The product was recovered by filtration, and washed with a mixture of CH₂Cl₂: ether (3:1 v/v) to yield a white amorphous powder; 16.70 g. The crude product was recrystallized from a mixture of CH₂Cl₂ (80 mL) and ether (80 mL) to give 12.40 g; mp 71-73 °C.

10 **Example 12. Preparation of 3-benzyl-oxazol-3-i um bromide**
2 g oxazole was reacted with 4.95 g benzyl bromide at room temperature for 2 hours and then overnight at 50°C. On cooling to room temperature, solids were filtered and dried. The yield was 3.1 g. The material was dissolved in ethanol and recrystallized with MTBE. The recrystallized compound had a melting point of 177-180°C and proton NMR spectra consistent with the structure 3-benzyl-oxazol-3-i um bromide. On analysis the compound contained 50.00% C, 4.04% H, 36.36% Br, and 5.08% N.

Example 13 - Cross-Linking Inhibition Assay

20 The following method was used to evaluate the ability of the compounds to inhibit the cross-linking of glycated bovine serum albumin (AGE-BSA) to rat tail tendon collagen-coated 96-well plates.

AGE-BSA was prepared by incubating BSA at a concentration of 200 mg per ml with 200 mM glucose in 0.4M sodium phosphate buffer, pH 7.4 at 37°C for 12 weeks. The glycated BSA was then extensively dialyzed against phosphate buffer solution (PBS) for 48 hours with additional 5 times buffer exchanges. The rat tail tendon collagen coated plate was blocked first with 300 microliters of Superbloc blocking buffer (Pierce Chemical, Rockford, IL) for one hour. The blocking solution was removed from the wells by washing the plate twice with phosphate buffered saline (PBS)-Tween 20 solution (0.05% Tween 20) using a NUNC-multiprobe (Nalge Nunc, Rochester, NY) or 30 Dynatech ELISA-plate (Dynatech, Alexandria, VA) washer. Cross-linking of AGE-BSA (1 to 10 microgram per well depending on the batch of AGE-BSA) to rat tail tendon collagen coated plate was performed with and without the testing compound dissolved in

PBS buffer at pH 7.4 at one or more desired concentrations by the addition of 50 microliters each of the AGE-BSA diluted in PBS or in the solution of test compound at 37°C for 4 hours. Unbrownned BSA in PBS buffer with or without testing compound were added to the separate wells as the blanks. The un-cross-linked AGE-BSA was then 5 removed by washing the wells three times with PBS-Tween buffer. The amount of AGE-BSA crosslinked to the tail tendon collagen-coated plate was then quantitated using a polyclonal antibody raised against AGE-RNase. After a one-hour incubation period, AGE antibody was removed by washing 4 times with PBS-Tween.

The bound AGE antibody was then detected with the addition of horseradish 10 peroxidase-conjugated secondary antibody—goat anti-rabbit immunoglobulin and incubation for 30 minutes. The substrate of 2,2-azino-di(3-ethylbenzthiazoline sulfonic acid) (ABTS chromogen) (Zymed Laboratories, Inc., South San Francisco, CA) was added. The reaction was allowed for an additional 15 minutes and the absorbance was read at 410 nm in a Dynatech plate reader.

15

Example 14 - Cross-Link Breaking Assay

To ascertain the ability of the compounds of the instant invention to break or reverse already formed advanced glycosylation endproducts, a sandwich enzyme immunoassay was applied. Generally, the assay utilizes collagen-coated 96 well 20 microtiter plates that are obtained commercially. AGE-modified protein (AGE-BSA) is incubated on the collagen-coated wells for four hours, is washed off the wells with PBS-Tween and solutions of the test compounds are added. Following an incubation period of 16 hours (37°C) cross-link-breaking is detected using an antibody raised against AGE-ribonuclease or with an antibody against BSA.

25

Preparation of solutions and buffers

Bovine Serum Albumin (Type V) (BSA) (from Calbiochem) solution was prepared as follows: 400 mg of Type V BSA (bovine serum albumin) was added for each ml of 0.4 M sodium phosphate buffer, pH 7.4. A 400 mM glucose solution was prepared by dissolving 7.2 grams of dextrose in 100 ml of 0.4 M sodium phosphate buffer, pH 7.4.

30

The BSA and glucose solutions were mixed 1:1 and incubated at 37°C for 12 weeks. The pH of the incubation mixture was monitored weekly and adjusted to pH 7.4 if necessary. After 12 weeks, the AGE-BSA solution was dialyzed against PBS for 48

10034722001
10034722002
10034722003
10034722004
10034722005
10034722006
10034722007
10034722008
10034722009
10034722010
10034722011
10034722012
10034722013
10034722014
10034722015
10034722016
10034722017
10034722018
10034722019
10034722020
10034722021
10034722022
10034722023
10034722024
10034722025
10034722026
10034722027
10034722028
10034722029
10034722030
10034722031
10034722032
10034722033
10034722034
10034722035
10034722036
10034722037
10034722038
10034722039
10034722040
10034722041
10034722042
10034722043
10034722044
10034722045
10034722046
10034722047
10034722048
10034722049
10034722050
10034722051
10034722052
10034722053
10034722054
10034722055
10034722056
10034722057
10034722058
10034722059
10034722060
10034722061
10034722062
10034722063
10034722064
10034722065
10034722066
10034722067
10034722068
10034722069
10034722070
10034722071
10034722072
10034722073
10034722074
10034722075
10034722076
10034722077
10034722078
10034722079
10034722080
10034722081
10034722082
10034722083
10034722084
10034722085
10034722086
10034722087
10034722088
10034722089
10034722090
10034722091
10034722092
10034722093
10034722094
10034722095
10034722096
10034722097
10034722098
10034722099
10034722100
10034722101
10034722102
10034722103
10034722104
10034722105
10034722106
10034722107
10034722108
10034722109
10034722110
10034722111
10034722112
10034722113
10034722114
10034722115
10034722116
10034722117
10034722118
10034722119
10034722120
10034722121
10034722122
10034722123
10034722124
10034722125
10034722126
10034722127
10034722128
10034722129
10034722130
10034722131
10034722132
10034722133
10034722134
10034722135
10034722136
10034722137
10034722138
10034722139
10034722140
10034722141
10034722142
10034722143
10034722144
10034722145
10034722146
10034722147
10034722148
10034722149
10034722150
10034722151
10034722152
10034722153
10034722154
10034722155
10034722156
10034722157
10034722158
10034722159
10034722160
10034722161
10034722162
10034722163
10034722164
10034722165
10034722166
10034722167
10034722168
10034722169
10034722170
10034722171
10034722172
10034722173
10034722174
10034722175
10034722176
10034722177
10034722178
10034722179
10034722180
10034722181
10034722182
10034722183
10034722184
10034722185
10034722186
10034722187
10034722188
10034722189
10034722190
10034722191
10034722192
10034722193
10034722194
10034722195
10034722196
10034722197
10034722198
10034722199
10034722200
10034722201
10034722202
10034722203
10034722204
10034722205
10034722206
10034722207
10034722208
10034722209
10034722210
10034722211
10034722212
10034722213
10034722214
10034722215
10034722216
10034722217
10034722218
10034722219
10034722220
10034722221
10034722222
10034722223
10034722224
10034722225
10034722226
10034722227
10034722228
10034722229
10034722230
10034722231
10034722232
10034722233
10034722234
10034722235
10034722236
10034722237
10034722238
10034722239
10034722240
10034722241
10034722242
10034722243
10034722244
10034722245
10034722246
10034722247
10034722248
10034722249
10034722250
10034722251
10034722252
10034722253
10034722254
10034722255
10034722256
10034722257
10034722258
10034722259
10034722260
10034722261
10034722262
10034722263
10034722264
10034722265
10034722266
10034722267
10034722268
10034722269
10034722270
10034722271
10034722272
10034722273
10034722274
10034722275
10034722276
10034722277
10034722278
10034722279
10034722280
10034722281
10034722282
10034722283
10034722284
10034722285
10034722286
10034722287
10034722288
10034722289
10034722290
10034722291
10034722292
10034722293
10034722294
10034722295
10034722296
10034722297
10034722298
10034722299
10034722300
10034722301
10034722302
10034722303
10034722304
10034722305
10034722306
10034722307
10034722308
10034722309
10034722310
10034722311
10034722312
10034722313
10034722314
10034722315
10034722316
10034722317
10034722318
10034722319
10034722320
10034722321
10034722322
10034722323
10034722324
10034722325
10034722326
10034722327
10034722328
10034722329
10034722330
10034722331
10034722332
10034722333
10034722334
10034722335
10034722336
10034722337
10034722338
10034722339
10034722340
10034722341
10034722342
10034722343
10034722344
10034722345
10034722346
10034722347
10034722348
10034722349
10034722350
10034722351
10034722352
10034722353
10034722354
10034722355
10034722356
10034722357
10034722358
10034722359
10034722360
10034722361
10034722362
10034722363
10034722364
10034722365
10034722366
10034722367
10034722368
10034722369
10034722370
10034722371
10034722372
10034722373
10034722374
10034722375
10034722376
10034722377
10034722378
10034722379
10034722380
10034722381
10034722382
10034722383
10034722384
10034722385
10034722386
10034722387
10034722388
10034722389
10034722390
10034722391
10034722392
10034722393
10034722394
10034722395
10034722396
10034722397
10034722398
10034722399
10034722400
10034722401
10034722402
10034722403
10034722404
10034722405
10034722406
10034722407
10034722408
10034722409
10034722410
10034722411
10034722412
10034722413
10034722414
10034722415
10034722416
10034722417
10034722418
10034722419
10034722420
10034722421
10034722422
10034722423
10034722424
10034722425
10034722426
10034722427
10034722428
10034722429
10034722430
10034722431
10034722432
10034722433
10034722434
10034722435
10034722436
10034722437
10034722438
10034722439
10034722440
10034722441
10034722442
10034722443
10034722444
10034722445
10034722446
10034722447
10034722448
10034722449
10034722450
10034722451
10034722452
10034722453
10034722454
10034722455
10034722456
10034722457
10034722458
10034722459
10034722460
10034722461
10034722462
10034722463
10034722464
10034722465
10034722466
10034722467
10034722468
10034722469
10034722470
10034722471
10034722472
10034722473
10034722474
10034722475
10034722476
10034722477
10034722478
10034722479
10034722480
10034722481
10034722482
10034722483
10034722484
10034722485
10034722486
10034722487
10034722488
10034722489
10034722490
10034722491
10034722492
10034722493
10034722494
10034722495
10034722496
10034722497
10034722498
10034722499
10034722500
10034722501
10034722502
10034722503
10034722504
10034722505
10034722506
10034722507
10034722508
10034722509
10034722510
10034722511
10034722512
10034722513
10034722514
10034722515
10034722516
10034722517
10034722518
10034722519
10034722520
10034722521
10034722522
10034722523
10034722524
10034722525
10034722526
10034722527
10034722528
10034722529
10034722530
10034722531
10034722532
10034722533
10034722534
10034722535
10034722536
10034722537
10034722538
10034722539
10034722540
10034722541
10034722542
10034722543
10034722544
10034722545
10034722546
10034722547
10034722548
10034722549
10034722550
10034722551
10034722552
10034722553
10034722554
10034722555
10034722556
10034722557
10034722558
10034722559
10034722560
10034722561
10034722562
10034722563
10034722564
10034722565
10034722566
10034722567
10034722568
10034722569
10034722570
10034722571
10034722572
10034722573
10034722574
10034722575
10034722576
10034722577
10034722578
10034722579
10034722580
10034722581
10034722582
10034722583
10034722584
10034722585
10034722586
10034722587
10034722588
10034722589
10034722590
10034722591
10034722592
10034722593
10034722594
10034722595
10034722596
10034722597
10034722598
10034722599
10034722600
10034722601
10034722602
10034722603
10034722604
10034722605
10034722606
10034722607
10034722608
10034722609
10034722610
10034722611
10034722612
10034722613
10034722614
10034722615
10034722616
10034722617
10034722618
10034722619
10034722620
10034722621
10034722622
10034722623
10034722624
10034722625
10034722626
10034722627
10034722628
10034722629
10034722630
10034722631
10034722632
10034722633
10034722634
10034722635
10034722636
10034722637
10034722638
10034722639
10034722640
10034722641
10034722642
10034722643
10034722644
10034722645
10034722646
10034722647
10034722648
10034722649
10034722650
10034722651
10034722652
10034722653
10034722654
10034722655
10034722656
10034722657
10034722658
10034722659
10034722660
10034722661
10034722662
10034722663
10034722664
10034722665
10034722666
10034722667
10034722668
10034722669
10034722670
10034722671
10034722672
10034722673
10034722674
10034722675
10034722676
10034722677
10034722678
10034722679
10034722680
10034722681
10034722682
10034722683
10034722684
10034722685
10034722686
10034722687
10034722688
10034722689
10034722690
10034722691
10034722692
10034722693
10034722694
10034722695
10034722696
10034722697
10034722698
10034722699
10034722700
10034722701
10034722702
10034722703
10034722704
10034722705
10034722706
10034722707
10034722708
10034722709
10034722710
10034722711
10034722712
10034722713
10034722714
10034722715
10034722716
10034722717
10034722718
10034722719
10034722720
10034722721
10034722722
10034722723
10034722724
10034722725
10034722726
10034722727
10034722728
10034722729
10034722730
10034722731
10034722732
10034722733
10034722734
10034722735
10034722736
10034722737
10034722738
10034722739
10034722740
10034722741
10034722742
10034722743
10034722744
10034722745
10034722746
10034722747
10034722748
10034722749
10034722750
10034722751
10034722752
10034722753
10034722754
10034722755
10034722756
10034722757
10034722758
10034722759
10034722760
10034722761
10034722762
10034722763
10034722764
10034722765
10034722766
10034722767
10034722768
10034722769
10034722770
10034722771
10034722772
10034722773
10034722774
10034722775
10034722776
10034722777
10034722778
10034722779
10034722780
10034722781
10034722782
10034722783
10034722784
10034722785
10034722786
10034722787
10034722788
10034722789
10034722790
10034722791
10034722792
10034722793
10034722794
10034722795
10034722796
10034

hours with four buffer changes, each at a 1:500 ratio of solution to dialysis buffer. Protein concentration was determined by the micro-Lowry method. The AGE-BSA stock solution was aliquoted and stored at -20°C.

Test compounds were dissolved in PBS and the pH was adjusted to pH 7.4, if necessary. AGE-BSA stock solution was diluted in PBS to measure maximum crosslinking and in the inhibitor solution for testing inhibitory activity of compounds. The concentration of AGE-BSA necessary to achieve the optimum sensitivity was determined by initial titration of each lot of AGE-BSA.

Substrates for detection of secondary antibody binding were prepared by diluting the HRP substrate buffer (Zymed) 1:10 in distilled water and mixing with ABTS chromogen (Zymed) 1:50 just prior to use.

Assay Procedures

Biocoat plates were blocked with 300 microliters of Superbloc (Pierce Chemical). Plates were blocked for one hour at room temperature and were washed with PBS-Tween (0.05% v/v) three times with the Dynatech platewasher before addition of test reagents.

The first three wells of the Biocoat plate were used for the reagent blank. Fifty microliters of solutions AGE-BSA were added to test wells in triplicate and only PBS in blank wells. The plate was incubated at 37°C for four hours and washed with PBS-Tween three times. Fifty microliters of PBS was added to the control wells and 50 microliters of the test prospective agent was added to the test wells and blank. The plate was incubated overnight (approximately 16 hours) with prospective agent, followed by washing in PBS before addition of primary antibody.

(Prior to use, each lot of primary antibody, either anti-BSA or anti-RNase, was tested for optimum binding capacity in this assay by preparing serial dilutions (1:500 to 1:2000) and plating 50 microliters of each dilution in the wells of Biocoat plates.

Optimum primary antibody was determined from saturation kinetics.) Fifty microliters of primary antibody of appropriate dilution, was added and incubated for one hour at room temperature. The plate was then washed with PBS-Tween.

Plates were incubated with the secondary antibody, HRP-(Goat-anti-rabbit), which was diluted 1:4000 in PBS and used as the final secondary antibody. The incubation was performed at room temperature for thirty minutes.

Detection of maximum crosslinking and breaking of AGE crosslinking was performed as follows. HRP substrate (100 microliter) was added to each well of the plate and was incubated at 37°C for fifteen minutes. Readings were taken in the Dynatech ELISA-plate reader.

5

Definition

Heterocycle. Except where heteroaryl is separately recited for the same substituent, the term "heterocycle" includes heteroaryl.

10 All publications and references, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference in their entirety as if each individual publication or reference were specifically and individually indicated to be incorporated by reference herein as being fully set forth. Any patent application to which this application claims priority is also incorporated by reference
15 herein in its entirety in the manner described above for publications and references.

While this invention has been described with an emphasis upon preferred embodiments, it will be obvious to those of ordinary skill in the art that variations in the preferred devices and methods may be used and that it is intended that the invention may be practiced otherwise than as specifically described herein. Accordingly, this invention
20 includes all modifications encompassed within the spirit and scope of the invention as defined by the claims that follow.

100-244-274-12